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Helsinki, Finland

THERAPEUTIC FACTORS CONTRIBUTING TO THE LONG-TERM SURVIVAL OF ACUTE CORONARY SYNDROME PATIENTS

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DOCTORAL DISSERTATION

To be presented, with the permission of the Faculty of Medicine of the University of Helsinki, for public examination in Biomedicum, Lecture Hall 1, on Friday November 13th, 2020, at 12 noon.

Helsinki, 2020

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ISBN 978-951-51-6718-7 (paperback)
ISBN 978-951-51-6719-4 (PDF)
http://ethesis.helsinki.fi

Unigrafia Oy
Helsinki, 2020

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'We choose to go to the Moon…We choose to go to the Moon in this decade and do the other things, not because they are easy, but because they are hard.'

—John F. Kennedy

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles:

I Allonen J, Nieminen MS, Lokki M, Parkkonen O, Vaara S, Perola M, Hiekkalinna T, Strandberg TE, Sinisalo J. Mortality rate increases steeply with nonadherence to statin therapy in patients with acute coronary syndrome. *Clin Cardio*l. 2012 Nov;35(11): E22–7.

II Allonen J, Nieminen MS, Hiippala S, Sinisalo J. Relation of Use of Red Blood Cell Transfusion After Acute Coronary Syndrome to Long-Term Mortality. *Am J Cardiol.* 2018 June 15;121(12):1496–1504.

III Allonen J, Nieminen MS, Sinisalo J. Poor adherence to beta-blockers is associated with increased long-term mortality even beyond the first year after an acute coronary syndrome event. *Ann Med*. 2020 Mar 17:1–11

IV Allonen J, Sinisalo J. The use of non-steroidal antiinflammatory drugs is still common among acute coronary syndrome patients and strongly associated with recurrent myocardial infarction and mortality. (Submitted to *Clinical Cardiology*)

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ABBREVIATIONS

1YLS	One-year landmark survival
ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate receptor
AHA	American Heart Association
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
ARC-HBR	Academic Research Consortium for High-Bleeding Risk
ATC	Anatomical therapeutic chemical
BARC	Bleeding Academic Research Consortium
BETAMI	Beta-blocker Treatment After Acute Myocardial Infarction in Patients Without Reduced Left-Ventricular Systolic Function
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CAG	Coronary angiography
CAPITAL-RCT	Carvedilol Post-Intervention Long-Term Administration in a Large-Scale Randomised Controlled Trial
CAPRICORN	Carvedilol Post-infarction Survival Control in Left-Ventricular Dysfunction
CCS	Canadian Cardiovascular Society
CI	Confidence interval
CKD	Chronic kidney disease
COROGENE	Genetic Predisposition for Coronary Artery Disease
COX	Cyclooxygenase
CV	Cardiovascular
CYP	Cytochrome P
DAPT	Dual antiplatelet therapy
DDD	Defined daily dose
DM	Diabetes mellitus
ECG	Electrocardiogram
ESC	European Society of Cardiology
GLP1-RA	Glucagon-like peptide 1 receptor agonist
GUSTO	Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
Hb	Haemoglobin
HDL-C	High-density lipoprotein cholesterol

HF	Heart failure
HILMO	Care Register for Health Care
HMG-CoA	3-Hydroxy-3-methylglutaryl-coenzyme A
HR	Hazard ratio
HUS	Hospital District of Helsinki and Uusimaa
ICU	Intensive care unit
IL	Interleukin
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
IU	International unit
LBBB	Left-bundle branch block
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)
LV	Left ventricular
LVEF	Left-ventricular ejection fraction
MI	Myocardial infarction
NSAID	Nonsteroidal antiinflammatory drugs
NSTE-ACS	Non-ST-elevation acute coronary syndrome
NSTEMI	Non-ST-elevation myocardial infarction
OR	Odds ratio
OS	Overall survival
OTC	Over-the-counter
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PGE	Prostaglandin E
PGH	Prostaglandin H
PGI	Prostacyclin
RAA	Renin-angiotensin-aldosteron
RBC	Red blood cell
RCT	Randomised controlled trial
SD	Standard deviation
SGLT	Sodium-glucose cotransportor 2
SII	Social Insurance Institution of Finland
STEMI	ST-elevation myocardial infarction
TC	Total cholesterol
TIMI	Thrombolysis in myocardial infarction
TnI	Cardiac troponin I
TnT	Cardiac troponin T
TRIM	Transfusion-related immune modulation
TXA	Thromboxane
UAP	Unstable angina pectoris
VIF	Variance inflation factor
WHO	World Health Organisation

ABSTRACT

Background and aims

In recent decades, prognosis amongst acute coronary syndrome (ACS) patients has improved. However, adherence to secondary prevention therapies recommended by guidelines appears insufficient, thereby affecting ACS patients' survival, particularly in relation to statins. Furthermore, the prognostic benefit of widely used β-blockers following ACS, especially amongst low-risk patients, has been disputed. In addition, despite contraindications, ACS patients continue relying upon nonsteroidal antiinflammatory drugs (NSAIDs), which may prove even fatal. Increasingly, guidelines have been unable to establish recommendations for the safe use of red blood cell (RBC) transfusions in an ACS setting. Thus, this study aimed to explore the adherence rates to statins and β-blockers as well as the utilisation rate of prescription NSAIDs and their impact on long-term survival amongst ACS patients. Additionally, we sought to determine the effect of RBC transfusion therapy on ACS patients' long-term morbidity and mortality.

Material and methods

From 5294 consecutive patients undergoing a coronary angiography (CAG) between 2006 and 2008 in the Genetic Predisposition for Coronary Artery Disease Study (COROGENE), 2090 patients were initially diagnosed with ACS, upon which studies I through IV in this study are based. To assess the utilisation of prescription medications in studies I, III and IV, we obtained data from the Finnish Prescription Register of the Social Insurance Institute (SII) and gathered mortality figures with causes of death from Statistics Finland. In studies II through IV, the Care Register for Health Care (HILMO) from the Finnish Institute for Health and Welfare was used to assess the recurrence of hospitalisations for different reasons. In study II, we merged data on transfusions and haemoglobin (Hb) values from a comprehensive hospital transfusion registry of the Hospital District of Helsinki and Uusimaa (HUS). The primary endpoint in studies I through III was all-cause mortality, whilst in study IV we assessed composite endpoint of recurrent myocardial infarction (MI) and all-cause mortality. Median follow-up was 23 months in study I, 8.6 years in studies II and III and 8.7 years in study IV.

Main results

In study I when comparing regular statin users (61.7%, n = 1200/1945) to irregular users (33.5%, n = 651/1945) and nonusers (4.8%, n = 94/1945), we observed a stepwise increase in mortality (4.9%, 9.4% and 14.9%, respectively, $p < 0.001$). The relative risk of mortality was almost threefold higher for nonusers compared to regular users in a multivariable Cox proportional

hazards model [hazard ratio (HR) 2.70, (95% confidence interval (CI) 1.49–4.90), p = 0.001].

In study II, we compared RBC transfused patients (4.4%, n = 85/1937) to nontransfused patients (66.0%, n = 1278/1937). RBC transfused patients exhibited a worse long-term prognosis considering both absolute mortality (58.8% vs. 20.3%, p < 0.001) and an adjusted multivariable Cox regression model [HR 1.91 (95%CI 1.39–2.63), p < 0.001]. After matching 65 patients from each group in a 1:1 fashion based on their propensity score, results remained rather consistent [HR 2.70 (95%CI 1.48–4.95), p = 0.001]. The inverse probability treatment weighted (IPTW) model further confirmed our results [HR 2.07 (95%CI 1.38–3.11), p < 0.001].

In study III, we assessed adherence to β-blockers separately for each yearly period of follow-up and examined adherence as a time-dependent variable in the Cox proportional hazards model. In a multivariable model adjusted for the concomitant use of other secondary prevention medications, nonadherence to β-blockers associated with an increased risk of mortality for both overall survival (OS) [HR 1.84 (95%CI 1.51–2.24), p < 0.001] and on one-year landmark survival (1YLS) [HR 1.74 (95%CI 1.41–2.14), p < 0.001]. The effect on all-cause mortality was also seen within the low-risk patient subgroup [HR 1.60 (95%CI 1.16–2.21), p = 0.004].

As many as 54.3% (n = 1042/1919) of patients filled at least one NSAID prescription during the entire follow-up period in study IV. Yearly use, defined as ≥1 prescription filled per year, decreased slightly from a peak of 22.4% during the second year to 14.5% during the eighth year of follow-up. Current use of NSAID (4.6%, n = 88/1919), defined by the number of days' supply for the most recent prescription filled lasting up to at least 30 days before the outcome event, was associated with an increased risk of a composite outcome in a mutltivariable adjusted logistic regression model [OR 1.75 (95%CI 1.10–2.78), p = 0.019]. However, we observed no difference in the absolute rates of the composite outcome when comparing current users with nonusers (53.4% vs. 48.5%, p = 0.368). The finding was repeated in the multivariable analyses amongst low-risk patients [OR 2.03 (95%CI 1.19–3.48), p = 0.010].

Conclusions

The risk of mortality appears to incrementaly rise with the level of nonadherence to statins amongst ACS patients. Nonadherence to β-blockers also associated with an increased risk of death, even beyond the first year following an ACS event. Furthermore, low-risk patients also appear to benefit from continuous β-blocker therapy. Alarmingly, despite contraindications many ACS patients continue using prescribed NSAIDs and their use associated with an increased risk of recurrent MI and death. Finally, RBC transfusion associated with a poorer prognosis amongst ACS patients, even during long-term follow-up.

1 INTRODUCTION

Much has been achieved in recent decades towards improving both primary prevention of and treatment for coronary artery disease (CAD) in general. Yet, whilst slightly declining, ischemic heart disease remains the leading cause of death in Finland, Europe and globally.[1-3] The incidence of a first myocardial infarction (MI) has decreased due to the evolution of effective primary prevention and an increased knowledge of the disease and its risk factors. Diagnostics, treatment algoritms, medications as well as revascularisation techniques used to treat acute coronary syndrome (ACS) patients have also evolved substantially in the last 20 years. These measures have improved both the short- and long-term outcomes for coronary patients. Moreover, with advanced treatment options, MI amongst increasingly fragile and older patients can also now be treated.[4-8]

However, effective antithrombotic medications carry the risk of bleeding. In recent years, increasing attention has been paid to bleeding complications and their effect on ACS patient survival.[9,10] Red blood cell (RBC) transfusion has been widely used to correct anaemic and bleeding patients' haemoglobin (Hb) levels to ensure oxydation of a vulnerable myocardium during ACS.[11] Recenlty, however, in addition to adverse reactions, long-term morbidity and mortality have been linked to RBC transfusion treatment. Aside from ACS patients, guidelines recommend a conservative approach to RBC transfusion in practically every setting. Amongst ACS patients, however, studies remain contradictory and, therefore, conclusive recommendations are lacking.[12-14]

There is room for a magnitude of improvements to optimal secondary prevention, particularly related to adherence to evidence-based medical therapies. Recent studies show that 5% to 20% of MI patients do not use the medications prescribed to them.[15-17] Furthermore, as many as 20% to 50% of patients use medications irregularly or discontinue them within the first years of follow-up. During follow-up, nonadherence increases further. This pattern is seen within all secondary preventive medications, but particularly with statins.[18-20]

In addition, given the widespread use of modern revascularisation therapies, the role of well-known and commonly used β-adrenergic receptor blockers (simply, β-blockers) in the treatment of ACS patients, particularly amongst those with a low residual risk, has been questioned.[21] Only a few randomised controlled trials (RCTs) have been conducted in the reperfusion era, with contradictory findings.[22,23] Observational studies have provided evidence both for and against their use amongst patients with preserved left-ventricular (LV) function. Yet, some studies propose that, amongst such patients, 1 to 3 years of therapy would be sufficient, whereas other studies recommend permanent β-blocker treatment for all ACS patients.[24-34] Thus, consensus has yet to be reached on this topic as well.

Nonsteroidal antiinflammatory drugs (NSAIDs) represent the most broadly used medications to ease pain, fever and inflammation.[35] Amongst coronary patients, comorbidities often requiring pain relief, such as rheumatoid arthritis or arthrosis, remain fairly common. Following the advent of cyclooxygenase (COX)-2 selective coxibs at the beginning of the twenty-first century, the adverse cardiac effects associated with all NSAIDs were identified.[36-41] These findings led to restrictions and recommendations against their use amongst cardiac patients.[42,43] Yet, alarmingly many ACS patients continue to use NSAIDs.[35,43-48] To what extent and with what sort of results remain unclear, at least in Finland.

Thus, this study aimed to investigate these issues contributing to ACS patients' long-term survival in the modern reperfusion era. We sought to examine the utilisation of prognostic secondary prevention medications, namely, statins and β-blockers, as well as potentially life-threatening NSAIDs. Furthermore, we investigated their effect on ACS patients' morbidity and mortality. In addition, we sought to determine the prevalence and impact of RBC transfusion treatment on long-term outcomes.

2 REVIEW OF THE LITERATURE

2.1 ACUTE CORONARY SYNDROME

Typically, a patient presenting with acute chest pain or shortness of breath initiates a diagnostic and treatment cascade for suspected ACS. As the name of the syndrome depicts, the setting has evolved rapidly and the propable culprit of the incident lies within the coronary arteries. Described in more detail below, ACS falls into two main categories based on clinical findings as well as pathophysiological and prognostic features. These are:

1) ST-segment elevation myocardial infarction (STEMI) and
2) Non-ST-segment elevation acute coronary syndrome (NSTE-ACS), which further falls into the final diagnoses of:
    a. Non-ST-segment elevation myocardial infarction (NSTEMI) and
    b. Unstable angina pectoris (UAP).

2.1.1 EPIDEMIOLOGY

Despite significant achievements in both preventing and treating CAD and ACS, ischemic heart disease remains the leading cause of death worldwide, accounting for 16.6% of all deaths globally, or about 9.4 million deaths annually.[1] The World Health Organisation (WHO) estimated that in 2016 almost 200 000 years of life were lost globally due to ischemic heart disease, rising from roughly 150 000 in 2000.[49] Although coronary mortality in Europe has declined in the last three decades, around 1.8 million deaths still result from CAD in Europe, corresponding to 20% of all deaths.[3,50] Furthermore, an estimated 15% to 20% of all deaths result from sudden cardiac death (SCD), a death that is unexpected and which typically occurs outside of a hospital.[51-54] SCD accounts for as many as half of all cardiac deaths globally[55] and is primarily thought to result from a fatal arrhythmia, such as ventricular fibrillation, often triggered by the onset of acute coronary syndrome. Approximately 60% to 80% of SCDs result from CAD.[55,56] For instance, a recent Finnish study examining individuals suffering an SCD caused by ischemic heart disease, found that an autopsy revealed about 42% of previously CAD-naïve patients suffered a silent myocardial infarction.[52] Additionally, about 25% to 35% of patients suffering from acute MI, typically STEMI, die of SCD before reaching a medical facility.[57]

In Finland, 20% of all deaths are caused by CAD; in 2018, there were roughly 10 000 coronary deaths.[2] Furthermore, 60 000 patients are admitted to hospital annually because of CAD, about 15 000 patients due to an acute cardiac event. Whilst the incidence of ACS has steadily declined since the 1990s, that rate has remained stable for the last 10 years in Finland.[58]

However, when examining different subtypes of ACS, in recent years, the relative incidence of STEMI has decreased, yet NSTEMI increased.[6,8] Short-term mortality appears greater for STEMI patients when compared to NSTEMI patients, although both short- and long-term mortalities, particularly for STEMI, continue to decline.[59,60] In-hospital mortality amongst ACS patients in European countries varies from 4.5% to 15%, standing at 6.5% in Finland in 2013.[50] Furthermore, 30-day short-term mortality following events ranged from around 2% to 8% amongst all ACS patients.[7,61] In the long term, differences in mortality rates between STEMI and NSTEMI appear to be narrowing, ranging from 8% to 10% 1 year after an event.[4,5,7,62-64] Amongst NSTE-ACS patients, long-term mortality is slightly greater than amongst STEMI patients, primarily explained by the older age and an increased comorbidity amongst NSTE-ACS patients.[65,66] In a Finnish registry study, the 1- and 3-year mortality of ACS patients surviving the first 28 days following an event were 12.9% and 26.5%, respectively. Accordingly, 21.6% and 32.7% of patients suffered a recurrent ACS within the 1- and 3-year follow-up periods, respectively.[67] The general decline in mortality caused by ACS is primarily due to evolving antithrombotic therapies, particularly the more frequent and sophisticated reperfusion therapy—namely, primary percutaneous coronary intervention (PCI)—as well as a greater emphasis on secondary prevention.[4,7] Post-ACS patients are also at a greater risk for an SCD. About 5% to 10% of these patients die of an SCD during the first year following an ACS.[68] Both an implantable cardioverter defibrillator (ICD) in select cases, as well as the wider availability and usage of automated external defibrillators (AEDs), have improved survival amongst ACS patients.[57,68-70]

2.1.2 PATHOPHYSIOLOGY

CAD is a local atherosclerotic disease of the coronary arteries with a similar pathology to other manifestations of atherosclerosis. Both high cholesterol and inflammation play key roles in the development of the disease.[71-73] Atherosclerotic plaque forms due to multiple factors, although hyperlipidaemia, namely, an increased consentration of low-density lipoprotein cholesterol (LDL-C), is essential.[74-76] Other major risk factors affecting the development of plaque include hypertension, diabetes mellitus (DM), smoking, being male and genetic factors.[77]

The formation of atherosclerotic plaques usually begins already during early adulthood. Typically, atherosclerotic plaques form along the inner curvatures and branching sites of the arterial tree due to shear stress caused by blood-flow mechanics. This mechanical stress induces changes in the endothelial metabolism, enabling cholesterol (especially, LDL-C) to accumulate along the thickened intimal layer of the artery to form fatty streaks.[78] Simply, LDL-C particles accumulate in the arterial intima and are modified by oxidation and aggregation, which, in turn, stimulates the innate

and adaptive immune response. Given this stimulation, adhesion molecules are expressed in the endothelium such that monocytes accumulate at the site and differentiate to the macrophages. This coincides with the accumulation of smooth muscle cells along the intimal layer of the coronary artery, causing it to increasingly thicken. The recruited macrophages become foam cells acting as lipid deposits. Furthermore, several layers of accumulated foam cells, the telltale signs of lipoprotein-driven inflammation, appear microscopically as fatty streaks. This phase is reversible; but, if the lipids continue accumulating, the fatty streaks become progressive atherosclerotic lesions.[75,79] The buildup of cholesterol along the arterial wall, in turn, induces the inflammatory processes, which both further promote the development of plaque into fibroatheroma and causes it to become more fragile.[80]

As the atherosclerotic plaque grows further, it may either become concentric or eccentric plaque (see Figure 1).[74,75] Concentric plaque is usually stable, with a small lipid core and thick fibrous cap at the top. Concentric plaque causes the arterial lumen to narrow as the fibrous cap at the top thickens due to continous erosion and healing in the endothelium.[75,81,82] In turn, in eccentric plaque with a large necrotic lipidous core, the fibrous cap is thinner whereby positive remodelling causes it to grow outwards without affecting the luminal cross-section in the same manner.[74] Typically, the former associates with stable coronary disease and causes symptoms during physical stress as oxygen demand in the myocardium increases. Yet, the blood flow remains inadequate due to stenosis of the arterial lumen. Ultimately, even a tiny thrombosis provoked by endothelial erosion may occlude the remainder of the free lumen and provoke ACS, usually NSTEMI or UAP.[81,83] Typically, in this situation, the thrombus forming is intramural, representing a platelet-rich 'white' thrombus. However, fibrin-rich 'white' thrombi have also been discovered in recent *in vivo* studies.[84]

By contrast, eccentric plaque may become symptomatic for the first time when its fragile, thin fibrous cap ruptures, exposing the highly thrombogenic lipid core, collagen and tissue factor, triggering the platelets to accumulate and activate. Concomitantly, the coagulation cascade is activated, converting fibrinogen into fibrin. These events initiate the formation of thrombus. Initially, the thrombus primarily consists of aggregated platelets and is macroscopically characterised as a fresh 'white' thrombus. As the thrombus grows, it becomes more fibrin-rich, and stabilises as an 'older' red thrombus, such that red blood cells and inflammatory cells become entrapped in the fibrin network.[85-87] Ultimately, the thrombus may occlude the entire lumen of the artery, thereby blocking the flow of blood and oxygen to the myocardium, leading to an acute MI, typically, STEMI.[74,88]

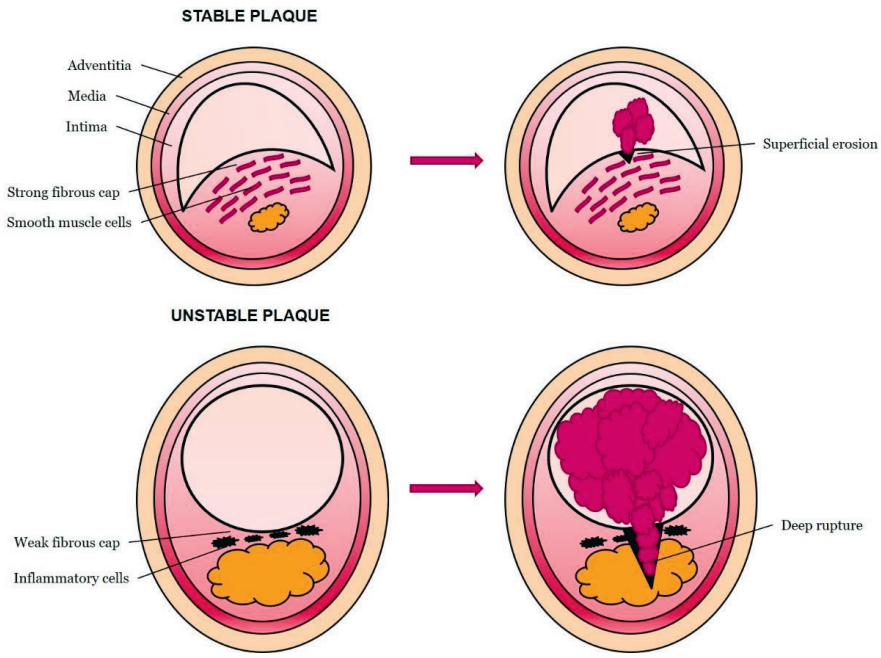

Figure 1 **Illustration of atherosclerotic plaque types.** Stable, concentric plaque with the subsequent superficial erosion of the endothelium and unstable, eccentric plaque with the complication of a deep rupture and occluding thrombosis.

2.1.3 RISK FACTORS

Atherosclerosis and, thus, CAD and ACS result from a number of risk factors.[77,89] All current guidelines suggest repeated systematic assessment of a patient's total cardiovascular (CV) risk to identify those at an increased risk due to their condition (e.g., documented CV disease, DM, renal disease, dyslipidaemia, smoking, hypertension and familial history), as well as amongst previously healthy adults over 40 years of age.[90-92] Based on a total risk assessment, each risk factor should be treated with either lifestyle management or drug intervention depending on the individual risk level.[90]

Dyslipidaemia with elevated cholesterol levels, especially LDL-C, is a crucial risk factor for CAD.[76,93-96] LDL-C accumulates in the coronary arteries when serum LDL-C levels are elevated. Moreover, elevated LDL-C appears to also associate with the inflammatory processes involved in CAD.[73,97] In addition to elevated LDL-C levels, high total cholesterol (TC) levels, low high-density lipoprotein (HDL-C) and a high TC/HDL-C ratio associate with an increased risk for ACS, particularly amongst men.[94,98] Triglycerides, however, do not appear to independently affect CAD risk on their own, but instead highly associate with other CV risk factors, such as obesity and DM.[91,97] Different types of treatments for dyslipidaemia have been historically

attempted, but only those attempting to lower the LDL-C concentration have demonstrably reduced the risk of MI, even with a direct proportionality to an absolute reduction in the LDL-C concentration.[99-101]

Hypertension represents one of the most common diseases and a major risk factor for CAD and ACS globally.[102,103] Elevated blood pressure not only affects the endothelial function of the arteries in favour of atherosclerotic plaque formation, but also puts the myocardium under an increased oxygen demand by increasing the heart's workload.[73,104] Both of these raise the risk of ACS, representing one of the reasons why hypertension should be treated aggressively.

One of the major CV risk factors, although declining at least in Europe, remains tobacco smoking. Smoking causes oxidative stress, endothelial dysfunction, inflammation and carries a strong prothrombotic effect, thus significantly increasing the risk of acute MI.[90,105,106] Smokers, particularly young women, amongst whom smoking is increasing, exhibit up to a three-times higher risk for MI.[90,107]

DM represents a signficiant independent risk factor for CAD and atherosclerosis in general. DM alone increases the risk of vascular complications twofold.[108] Diabetes, irrespective of type (type 2 being the most common), affects the pathophysiology of CAD, by, for instance, inducing inflammation and oxidative stress through atherosclerotic plaque.[109]

Although an independent risk factor itself, obesity also increases the incidence of DM, hypertension and dyslipidaemia.[90,110] All of these combine to form a metabolic syndrome, which today is alarmingly common. As with many of others, the primary effect of obesity on CV risk is mediated through the promotion of inflammation.[73]

In addition, genetic factors affect the course of atherosclerosis and ACS. In recent decades, their role has been examined in more detail.[111-114] In addition to the individual genetic or epigenetic differences, different ethnic origins, ages and being male have previously associated with an elevated risk for CAD and MI.[50]

Moreover, socioeconomic status, poverty, physical inactivity and a vegetable-poor diet demonstrably increase CVD risk and should likewise be addressed in the complete risk assessment and treatment of CAD patients.[89,90]

Whilst many of the risk factors are similar for stable CAD and ACS pathologically, some are more specifically bound to ACS. For instance, habitual physical activity has been shown to reduce the baseline risk of CAD, although the risk of ACS and SCD is transiently elevated during vigorous episodes of physical activity, such as exercise. However, this risk diminishes through regular exercise. Other specific triggers for ACS have been previously identified and include sexual activity, respiratory and urinary tract infections as well as chemical triggers such as caffeine, alcohol, marijuana and cocaine. Heavy meals have also been associated with an increased risk of ACS. In addition, psychological triggers such as anger, depression, anxiety and work-related stress have been associated with the onset of ACS. Furthermore,

population-based stressful events such as earthquakes, terror attacks and war have been reported as population-wide triggers for ACS.[115]

2.1.4 SYMPTOMS, DIAGNOSIS AND CLASSIFICATION

The diagnosis of ACS is based on typical symptoms, electrocardiogram (ECG) findings and cardiac enzymes. The diagnostic measures and primary treatment parallel one another in order to minimise the delay from symptom onset to definitive care.[116,117] ACS is divided into two initial categories, STEMI and NSTE-ACS, which is further classified as NSTEMI and UAP based upon the levels of cardiac biomarkers (see Figure 2).[118] Since treatment patterns differ based on the type of ACS, it is crucial to make a prompt initial diagnosis, specifically distinguishing between STEMI and NSTE-ACS based on ECG findings, as described below.[118,119]

The most typical symptom of ACS is chest pain radiating to the neck, lower jaw or left arm. Less common symptoms include shortness of breath, nausea or vomiting, sweating, syncope, palpitations and fatigue. Atypical and mild, sometimes misleading symptoms are more common amongst diabetics, the elderly and women.[116,120,121] The spectrum of symptoms presenting with ACS is wide, ranging from symptomless to sudden death. In NSTE-ACS, however, typical presentations of anginal pain are categorised as 1.) prolonged (>20 min) pain at rest, 2.) new onset angina [class II or III of the Canadian Cardiovascular Society (CCS) classification],[122] 3.) recent destabilisation of previously stable angina (at least CCS III) or 4.) post-MI angina.[117]

Due to changes in the electric currents caused by ischemic myocardium, ECG—more precisely, a persistent elevation to the ST-segment along at least two contiguous leads or the appearance of a new left-bundle branch block (LBBB)—plays a crucial role in the primary differentiation between STEMI and NSTE-ACS.[116,123] Although an ECG might appear completely normal amongst NSTE-ACS patients, various ECG changes can also occur in NSTEMI and UAP, which include the depression of an ST segment, T-wave inversions, branch/fascicular blocks, a transient ST elevation or nonspecific minor changes.[117,118] If the initial diagnosis quickly derived from the ECG findings points to STEMI, emergency care should be provided without further delay as described in the next section. As opposed to STEMI and NSTEMI, no ischemic damage to the myocardium appears in UAP, which is clinically differentiated from the former by the absence of elevated cardiac biomarkers in the blood stream.[117] Currently, cardiac troponins T and I (TnT and TnI), prefereably with a high sensitivity, are more often used, serving as the most significant biomarkers in diagnosing myocardial ischemia.[124,125] As cardiac biomarkers in MI, troponins increase rapidly after the onset of symptoms, usually within the first hour, and typically remain elevated for several days. For an NSTEMI diagnosis, the European Society of Cardiology (ESC) guidelines recommend using the 'rule-in' and 'rule-out' algorithms. NSTEMI can be ruled-out either by a low level of high-sensitivity troponin (hs-cTn) already upon presentation

or within 1 hour if no relevant increase in hs-cTn is detected. To rule-in for NSTEMI, hs-cTn should be either at least moderately elevated at the zero hour, or a clear increase in the hs-cTn levels at one hour should be observed. High-sensitivity cardiac troponins allow the monitoring period between blood samples to decrease from three hours to one hour.[117] Furthermore, high-sensitivity troponins can even be used as point-of-care samples in emergency room settings without necessitating a central laboratory.[126]

The definition of MI has evolved in recent decades.[121] The latest universal definition of MI separates a myocardial injury as a unique entity. Based on this definition, the term myocardial injury should be used when evidence appears of elevated cardiac troponin values with at least one value falling above the 99th percentile of the upper reference limit. Injury is considered acute if a rise and/or fall occurs in the troponin values. The term acute myocardial infarction (AMI) should instead be used if the previous criteria accompany at least one of the following: symptoms of myocardial ischemia, new ischemic ECG changes, the development of pathological Q waves in ECG, imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology or the identification of a coronary thrombus through angiography or autopsy.[123] MI falls into five different classifications based on the cause of the ischemia and prognostic differences. Compared to type 1 with a thrombus in the coronary lumen, type 2 is defined by an imbalance between myocardial oxygen supply and demand unrelated to thrombosis. A type 3 MI occurs if a patient with symptoms suggesting myocardial ischemia dies before the myocardial injury was established, relying on biomarkers or later during an autopsy. Types 4 and 5 are procedure-related MIs, for percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), respectively.

After the initial diagnosis followed by primary medical treatment, a coronary angiography (CAG) both confirms the diagnosis as well as is used to treat the culprit of the cardiac event if indicated. For NSTE-ACS patients, the necessity and timing–immediate (<2 h), early (<24 h) and invasive (<72 h)–of invasive CAG should be based upon individual risk stratification. For STEMI patients, an immediate diagnostic CAG combined with revascularisation is crucial.[116,117]

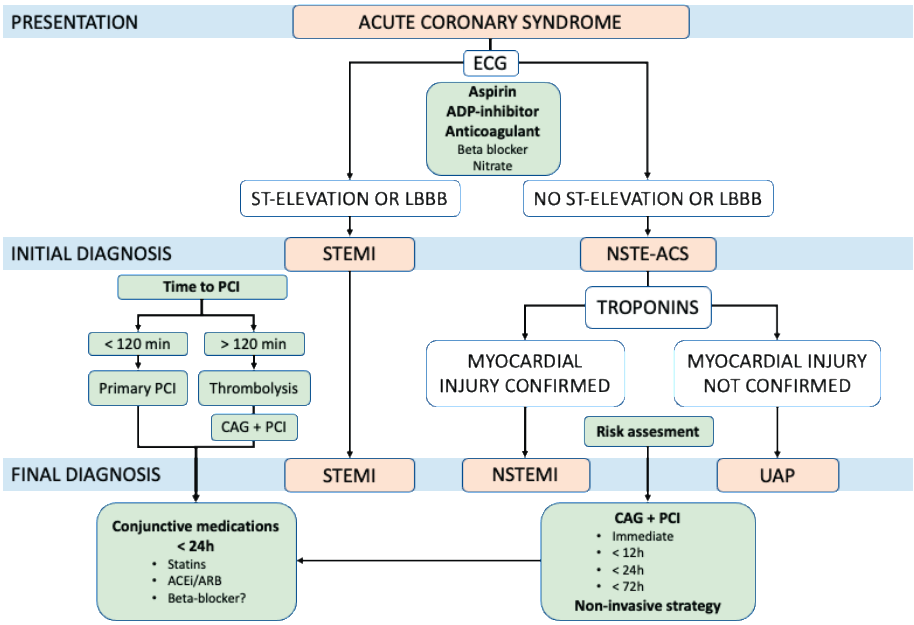

Figure 2 **Diagnostic and treatment patterns of acute coronary syndrome.** Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAG, coronary angiography; ECG, electrocardiogram; LBBB, left-bundle branch block; NSTE-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UA, unstable angina pectoris. Data adapted partially from White et al. 2008 with permission from Elsevier.[127]

2.1.5 TREATMENT

From the initial medical contact, ACS treatment runs parallel to both diagnostics and risk assessments (Figure 2). Differentiating between NSTE-ACS and STEMI remains crucial since revascularisation of the occluded artery in STEMI should be performed as quickly as possible. In STEMI, the decision regarding the appropriate reperfusion therapy should also be made quickly. Primary PCI preferably with a drug-eluting stent to the culprit lesion through radial access represents the first-line treatment of choice if possible, within the first two hours. STEMI patients should be immediately transferred to the cathetrisation laboratory from the field to minimise any delay in definite treatment. In centres caring for STEMI patients, this logistical and therapeutic algorithm should be established, reviewed and taught regularly. If primary PCI is not available within 120 min of diagnosing STEMI, thrombolysis, preferably at the incident site, followed by control CAG with the opportunity for rescue PCI serves as the second-best treatment option. For thrombolysis strategy, symptoms should not last longer than 12 h and contraindications should be absent. The efficacy of fibrinolysis decreases as the time from the onset of symptoms increases. Therefore, primary PCI should be considered as

an option if a patient presents late, particularly more than 3 h after sypmtom onset. After the initiation of thrombolysis, the patient should be transferred to a PCI centre, where CAG and PCI if indicated should be performed within 2 to 24 h of successful lysis.[116] If there are signs of unsuccessful fibrinolysis (recurrence of ST elevation and ongoing ischemic symptoms), immediate rescue PCI is indicated.[128] Typical findings for succesfull thrombolysis are >50% resolution in the ST segment within 60 to 90 min, reperfusion arrhythmia and the disappearance of chest pain.

For NSTE-ACS patients, the timing of CAG is based on an individual risk assessment depending upon symptoms and findings. CAG timing can vary from immediately to up to 72 hours. An immediate invasive strategy (CAG performed within 2 h) is indicated if an NSTE-ACS patient's risk is estimated as very high based on the ESC guidelines. The criteria for a very high-risk situation include amongst others haemodynamic instability, life-threatening arrhythmias and acute heart failure. If ST- or T-wave changes are dynamic, a rise or fall in troponins occurs or the Global Registry of Acute Coronary Events (GRACE) score exceeds 140, the patient is characterised as high risk and an early invasive strategy is recommended, where CAG is undertaken within the first 24 h. The maximum CAG delay for patients identified as needing an invasive strategy (intermediate risk) is 72 h. Intermediate risk factors include DM, renal insufficiency, LVEF <40%, prior PCI or CABG or a GRACE score between 110 and 139. A patient is characterised as low risk if they present with none of the above risk criteria, and an invasive strategy is indicated only in select situations if symptoms recur. Otherwise, a noninvasive stress test is recommended.[117] If the culprit lesion is anatomically unsuitable for PCI or a patient's haemodynamic situation is compromised due to, for instance, cardiogenic shock or a mechanical complication from MI, emergent CABG should be performed for AMI patients. However, given the limited evidence, the timing of nonemergent CABG for stabilised post-MI patients should be determined on an individual basis. Yet, a washout period of 3 to 7 days after discontinuing the adenosine diphosphate receptor (ADP) inhibitor from a dual antiplatelet therapy (DAPT) is recommended for both STEMI and NSTE-ACS patients.[116,117]

Contrary to differences in the revascularisation strategies between STEMI and NSTE-ACS patients, the standard medical care for both remains rather similar. According to various guidelines, antithrombotic therapy for an ACS patient irrespective of their final diagnoses comprises DAPT with aspirin and an ADP-receptor inhibitor (ticagrelor, prasugrel or clopidogrel) combined with a parenteral anticoagulant, whereby enoxaparin represents the drug of choice in Finland.[116-119,129,130] Aspirin should be given as soon as possible on site following the initial diagnosis. It is typically administered orally, although intravenous administration might offer quicker and a more complete effect on inhibiting platelet aggregation and thromboxane generation.[131] Although somewhat limited evidence exists for it, the early initiation of ADP inhibitors is also indicated.[132,133] Clopidogrel formerly represented the first-line

treatment as an ADP inhibitor in ACS treatment, but has recently been outpaced by faster acting ticagrelor and prasugrel with superior outcomes and greater potency.[134-136] Whilst accompanying a slightly higher risk of bleeding, if not contraindicated, those are now preffered ADP inhibitors (followed by clopidogrel) in ACS irrespective of the initial treatment strategy outlined in most recent guidelines.[130,137,138] However, for STEMI patients treated for thrombolysis, clopidogrel remains the recommended ADP inhibitor.[129] Ticagrelor and prasugrel have not been investigated in conjuction with thrombolysis and, therefore, should not be used for fibrinolysed patients.

When it comes to anticoagulation in ACS patients, slight differences exist in the guidelines. Finnish guidelines recommend low molecular–weight heparin—namely, enoxaparin—as the drug of choice for both NSTEMI and STEMI patients.[139,140] However, European guidelines emphasise the routine use of unfractioned heparin, whilst enoxaparin and bivalirudin (a direct thrombin inhibitor) serve as alternative options for anticoagulation in STEMI patients. For NSTE-ACS patients receiving medical treatment, the ESC guidelines recommend fondaparinux (a selective factor Xa inhibitor) before enoxaparin as a first-line anticoagulation agent. Finnish guidelines recommend case-specific consideration of a glycoprotein IIb/IIIa inhibitor for patients undergoing PCI.

Other conjunctive medical therapies used for both acute and long-term treatment of ACS consist of pain killers (namely, opioids titrated intravenously in an acute setting), β-blockers, nitrates, angiotensin-converting enzyme (ACE) inhibitors and statins. In an acute setting, β-blockers can be used both orally and intravenously (recommended) to control tachychardia and ischemic symptoms in the absence of signs of heart failure (HF), the development of cardiogenic shock or other contraindications. A randomised controlled trial (RCT) performed in 2005 found that an early intravenous β-blocker in AMI patients decreases the risk of reinfarction and ventricular fibrillation, but increased the risk of cardiogenic shock significantly.[141] Since then, multiple studies have reported somewhat similar findings.[142-144] Guidelines recommend the early administration of a β-blocker with appropriate caution to both NSTEMI and STEMI patients within the first 24 hours in the absence of contraindications. For haemodynamically stable STEMI patients, the intravenous administration of a β-blocker seems useful.[116-119] However, the definitive role of and effect on prognosis of β-blockers in acute treatment remain inconclusive, although early initiation seems to associate with both improved short- and long-term outcomes.[145,146] Nitrates appear not to affect survival or prognosis amongst AMI patients, but are administered to reduce ischemic symptoms, especially in patients with high blood pressure upon admission.[147] Furthermore, guidelines recommend the early initiation and continuation of intensive statin therapy to all ACS patients irrespective of their lipid profile.[93,148-150] In addition, statins have undeniably improved the prognosis of ACS patients in both short- and long-term follow-up.[151-153] ACE inhibitors or if ACE inhibitors are not tolerated angiotensin receptor blockers

(ARB) should also be initiated within the first 24 hours and continued, particularly for patients with any of the following: hypertension, DM, HF, left-ventricular ejection fraction (LVEF) under 40% or chronic kidney disease (CKD).[103,147,154-159]

2.1.6 SECONDARY PREVENTION

Despite the impressive achievements in treating ACS patients, these individuals remain at an elevated risk for recurrent MI and both all-cause and cardiac-specific mortality following an ACS event.[160-166] The elevated risk for both recurrent MI and death appears last indefinitely, although slightly decreases each subsequent year following an ACS event.[61,167] This risk, estimated based on the individual's risk profile, depends on multiple factors, most of which can be treated.[168] Secondary prevention is based on both changes to a patient's habits, such as exercising, weigth loss, smoking cessation and diet, but specifically relies on secondary prevention medications.[15,169] Treatment focuses on the same risk factors as primary prevention, although medical therapies play an even larger role in secondary risk reduction.[90,170] It is recommended that CV risk amongst ACS patients is evaluated annually following a cardiac event, even in asymptomatic cases. During the first year, at least two visits are recommended.[171] A recent observational study demonstrated that, although the prognosis for high-risk patients specifically has recently improved, such patients remain undertreated using secondary prevention medications.[172] Table 1 summarises the goals of treating different risk factors using their primary therapies.

Table 1. ***Risk factor targets and primary recommended therapies following ACS according to European guidelines.*** *Abbreviations: BMI, body mass index; CCB, calcium channel blocker; GLP1-R, glucagon-like peptide-1 receptor; LDL-C, low-density lipoprotein cholesterol; RAA, renin-angiotensin-aldosteron; SGLT2, sodium-glucose co-transporter 2. Data adapted from ESC guidelines.*[90,91,103,108,116,117,171]

Risk factor	Target	Primary recommended therapy
LDL-C	<1.4 mmol/l and ≥50% decrease from baseline	High-dose statin
Blood pressure	<140/90 mmHg If well-tolerated, <130/80 mmHg	1. RAA inhibitor + β-blocker/CCB 2. CCB + diuretic/β-blocker 3. β-blocker + diuretic
Diabetes	HbA1c < 7%	1. SGLT2 inhibitor 2. GLP1-R agonist
Body weight	BMI: 20–25 kg/m² Waist: <94cm (men) <80cm (women)	Diet, exercise, behavioural modifications
Smoking	No exposure at all	1. Follow-up support 2. Nicotine replacement 3. Varenicline, Bupropion
Diet	Healthy: low in saturated fat and salt, wholegrain, vegetables, fruit and fish	Behavioural modifications
Physical activity	≥150 min/week moderate or ≥75 min/week vigorous aerobic	Prescribed physical activity

One of the major secondary prevention therapies following ACS is DAPT, consisting of both aspirin and an ADP (P2Y12) inhibitor. Currently, guidelines recommend ticagrelor or prasugrel over clopidogrel; yet, by the time we recruited our cohort, clopidogrel stood as the drug of choice for all patients. For STEMI patients treated with primary PCI, treatment with DAPT should continue for 12 months.[116,119] For STEMI patients treated with fibrinolysis, European guidelines recommend (published 2017) extending DAPT for only one month if subsequent PCI is not performed (although expanding the duration to 12 months should be considered), and for 12 months if it was.[116] Published also in 2017, a European-focused update on DAPT recommends a 12-month treatment duration for all ACS patients without a high risk for bleeding, whether treated only medically with PCI or CABG, a recommendation similar to that for NSTE-ACS.[117,129] In addition, a US-focused update on the duration of DAPT published in 2016 by the American Heart

Association (AHA) and the American College of Cardiology (ACC) recommends a 12-month course of DAPT for all ACS patients, regardless of the acute treatment strategy.[130] For thrombolysed patients, all guidelines continue to recommend clopidogrel. For patients at a substantial risk for bleeding, a shortened therapy length of six months should be considered in both STEMI and NSTE-ACS, specifically if a drug-eluting stent was used for revascularisation. In addition, a concomitant proton pump inhibitor should be administered to patients at an increased risk of gastrointestinal bleeding. Following DAPT, aspirin should be used indefinitely and the continuation of DAPT as a long-term secondary prevention strategy for high-risk patients should be considered.[116,117,129,130,137,171] For ACS patients with a verified indication for oral anticoagulation (OAC), such as atrial fibrillation, mechanical heart valve or venous thromboembolism, triple therapy concisting of aspirin, clopidogrel and either NOAC or Warfarin should be used for up to six months, after which a dual therapy consisting of either an OAC/clopidogrel or aspirin/clopidogrel combination should be used for up to 12 months. After one year, only OAC is continued. If bleeding risks outweigh the ischemic risks, a triple therapy for only one month or a dual therapy with clopidogrel and OAC should be considered.[129]

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors or statins have unquestionably proven to decrease both short- and long-term mortality as well as the incidence of recurrent MI amongst post-ACS patients.[151] Guidelines encourage the early initiation of intensive statin therapy to all ACS patients irrespective of their lipid profile.[91,93,116-119,148,149] Based on the most recent European guidelines, statin therapy aims to achieve an LDL-C level <1.4 mmol/l or a 50% reduction if baseline LDL-C lies between 1.4 and 3.5 mmol/l. In post-ACS patients, the key message regarding LDL-C remains 'the lower the better'.[100,173,174] In Finland, the recommended target LDL-C in post-ACS patients remains <1.8 mmol/l, although national guidelines will likely become more strict in the near future in order to agree with European guidelines.[175] In the rare case of statin intolerance, ezetimibe should be considered as an optional lipid-lowering therapy. In addition, ezetimibe should be combined with high-intensity statin therapy if the LDL-C target level is not achieved after four to six weeks of treatment with a statin alone.[91,176] Furthermore, if this combination remains insufficiently effective, adding a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor—namely, evolocumab and alirocumab—is the final option. These represent the latest lipid-lowering medications on the market proven to lower the LDL-C concentration and, therefore, holding prognostic value.[177,178] The importance of statin therapy and specifically adherence to it are discussed in more detail below.

Despite the most significant evidence dating to the prereperfusion era, β-blockers are still used in the secondary prevention for CAD following ACS. European guidelines recommend a continuous β-blocker for all STEMI patients and those NSTE-ACS patients suffering from HF, arrhythmia or with

lowered LVEF. US guidelines recommend permanent β-blocker therapy for all MI patients other than those without HF or hypertension, for whom three years of treatment is considered sufficient.[116-119] The inconclusive role of β-blockers as a secondary prevention is addressed further below.

European guidelines recommend considering an angiotensin-converting enzyme (ACE) inhibitor for all STEMI patients, whilst strongly recommending one for both STEMI and NSTE-ACS patients with HF, LVEF under 40%, hypertension or diabetes.[116,117,147,155] As an individual risk factor for CAD and, thus, ACS, hypertension should be treated effectively to reach a target blood pressure of <130/80 mmHg amongst ACS patients. The algorithm in the ESC hypertension guidelines for the medical treatment of hypertension amongst CAD patients varies depending on the grade of hypertension and concomitant conditions (i.e., HF, atrial fibrillation and CKD), but is typically based on at least two agents in one pill initially (e.g., ACE inhibitor + β-blocker).[103] Recent European guidelines on stable coronary disease recommend an ACE inhibitor or ARB combined with a β-blocker for recent MI patients with hypertension.[171]

In addition, DM represents a substantial independent risk factor of CAD and ACS, whereby diabetic patients with CAD are considered very high-risk patients. Roughly 20% of CAD patients are previously diagnosed with DM, whilst prediabetes is even more common amongst both CAD and ACS patients. The targeted glycated HbA1c level for CAD patients should fall <7%. This can be achieved using both lifestyle management and tailored medical therapies.[108,171] The most conclusive evidence on reducing CV events and deaths amongst diabetic CAD patients results from sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP1-RAs), explaining their role as first-line recommendations followed by metformin.[108]

In addition to secondary preventive medical therapies, the prognosis for select ACS patients can also be improved by preventing an SCD caused by fatal arrhythmias using an implantable cardioverter defibrillator (ICD). ICD is recommended for the long-term management of ventricular arrhythmias amongst ACS patients with symptomatic heart failure and LVEF <35% despite optimal medical therapy for at least 3 months. At least 6 weeks should lapse from the event and the patient's expected survival should be at least 1 year in order to be eligible for an ICD implantation.[116]

2.2 STATINS

Given that the most important factor in the development of coronary artery plaque, and subsequently CAD, lies in the retention of LDL-C within the intimal layer of the artery wall, the most important prevention and treatment agents target lowering the concentration of LDL-C.[99] HMG-CoA reductase inhibitors or statins are the cornerstone medications in this instance, although other promising lipid-lowering therapies have recently emerged, which are

primarily utilised in tandem with statins to reduce LDL-C as much as possible.[177,178] The role of statins in secondary prevention following ACS was well-established long before our study. However, the effect of nonadherence on ACS patients' long-term survival remained scarcely investigated.[16,179-181]

2.2.1 PHARMACOLOGY

Statins inhibit HMG-CoA reductase, a rate-limiting enzyme in synthesising cholesterol in the liver. This reduces the intracellular concentration of cholesterol, which in turn promotes LDL-receptor expression on the cell membrane leading to the increased intake of LDL-C, eventually resulting in lowering the LDL-C concentration in the blood stream.[182] In this way, statins can reduce the LDL-C level by more than 50% from baseline, depending on the dosage administered.[91] In addition to being dose-dependent, a reduction in LDL-C is individual to which multiple genetic factors are also known to contribute.[173,183]

Although their primary effect is mediated through a reduction in LDL, statins carry positive albeit relatively minor effects on other lipids, such as HDL, triglycerides (TG) and Lipoprotein(a) [Lp(a)] as well.[184,185] In addition, the pleiotropic effects, such as antiinflammatory and antioxidant effects, have gained much attention given their discovery from *in vitro* studies, although their clinical meaning in CAD prevention remains inconclusive.[186,187]

In general, statins are very well-tolerated, but might cause specific adverse effects, of which the most feared whilst rare (1–3 cases/100 000 patient-years) is rhabdomyolysis.[188] More common adverse events include myopathy, elevation in the liver enzymes and the incidence of new-onset DM.[182,189] Statins can be categorised in many different ways, for instance, through their potency in lowering LDL-C, their chemical derivation (synthetic or fermentation), their lipo- vs. hydrophilic properties and their metabolism via different cytochrome enzymes [such as cytochrome P (CYP), to name a few].[190,191] These agent-specific characteristics amongst others affect both the potency in reducing LDL-C, but also the tolerability, possible adverse effects and interactions related to different statins.[182] Many drug–drug interactions have been observed with statins, primarily related to metabolism via CYP3A4, whilst many other CYPs are also involved.[91] In Finland, simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin are currently available on the market. Amongst these, the most-used statin during the recruitment of our study cohort was simvastatin, followed by atorvastatin and rosuvastatin.[192]

2.2.2 LONG-TERM USE OF STATINS FOLLOWING ACS

Following their introduction to the market for the treatment of hypercholesterolaemia in the 1980s, researchers amassed much evidence on the impact of statins on coronary patients' survival. Multiple meta-analyses from randomised controlled trials (RCTs) have demonstrated their efficacy on

both stable CAD as well as ACS patients.[151,174,193-197] In 2010, large meta-analyses concluded that a 20% reduction in CAD mortality accompanied each 1 mmol/l reduction in the LDL-C concentration comparing statin to no statin or high-intensity to low-intensity treatment.[93] Amongst ACS patients, guidelines recommend both early initiation and life-long high-intensity statin therapy. [148,149,152] Whilst cholesterol levels should be measured for risk assessment and further follow-up, statin therapy is indicated for every ACS patient regardless of lipid levels.[90,91,116,117] Statins also reduce the incidence of new HF amongst CAD and ACS patients.[198,199] Whether patients with HF but not CAD benefit from statins remains debatable, although a recent systematic review concluded that statins may improve CV outcomes amongst all HF patients, irrespective of their LVEF level and their HF aetiology.[200] However, two prior RCTs and a meta-analysis concluded that amongst HF patients no clear benefit results from statins in terms of CV mortality.[201-203]

Prior to our statin study, issues regarding adherence to secondary prevention therapies, specifically to statins, were observed.[180,181,204] Furthermore, in Finland at the beginning of the preceding decade, statins received unjustified negative media coverage, impacing public opinion on statins. Misinformation regarding their alleged adverse effects also spread.[205]

In separate studies, 5% to 20% of ACS patients did not initiate statin therapy following discharge, with another 13% discontinuing its use at 6 months. In addition, the adherence rate decreased during the follow-up, falling to about 40% to 75% at the 1- to 2-year mark, further falling to as low as 26% to 49% at the 5-year follow-up mark.[15,16,18,20,179,206,207] In a study analysing the persistence of statin therapy amongst new statin users in Finland, only 43.9% of patients remained adherent after 10 years.[19] However, the rate of statin discontinuation during the first year following treatment initiation decreased at least up to 2004 compared with discontinuation levels from 1995 initiators, in Finland.[208] Moreover, alongside increased in-hospital statin use, guidelines were generally better followed in 2003 than in 2001 based on the FINACS (Finnish Prospective Nation Wide Study on Acute Coronary Syndrome) I and II studies amongst NSTE-ACS patients.[209]

A discrepancy in the adherence rates comparing clinical trials and real-life practice was also noted.[210,211] Multiple factors affecting nonadherence, including genuine side effects, polypharmacy, viewing a medication as unnecessary and even the prescriber's personality, were identified. Proposals aimed at improving adherence were also investigated.[180,207,212,213] A delay in filling the first statin prescription following hospitalisation for ACS was identified as one indicator of a greater risk for future nonadherence.[214]

By the time of our study, however, the impact of nonadherence to statins on ACS patients' long-term mortality was rarely assessed.[17,20,215] Yet, these studies consistently reported around a 25% to 40% increase in the relative risk for all-cause mortality with nonadherence to statins. Moreover, meta-analyses identified an increased mortality with nonadherence to a placebo, both

highlighting the complexity of adherence *per se* as well as demonstrating the existence of a healthy adherer bias in adherence studies.[216]

After our study, several studies have assessed adherence to secondary prevention medications following ACS, reporting somewhat similar findings, regarding statin therapy, than studies conducted prior to ours.[217-223] Interestingly, however, a Cochrane review published in 2014 claimed that the initiation of statin therapy within 14 days of ACS onset rather than reducing unstable angina did not reduce mortality, stroke incidence or recurrence of MI within the first four months of use.[224] However, the authors noted that the prognostic effects of statins probably manifest only later than 4 months following ACS. In a European multicentre survey, on average about 85% of CAD/ACS patients used a statin at the follow-up interview, a median of 1.35 years after the index event of PCI, CABG or ACS. However, a marked variation in statin adherence between countries was observed, ranging from 73.5% to 96.1%, whereby Finland clearly fell below the average at 81.9%.[225] The 1-year adherence rate to statins following ACS, measured as MPR >80% based on the defined daily dose (DDD), differed significantly between US and Hong Kong cohorts at 78.2% and 90.0%, respectively.

Interventions aimed at improving adherence have also been examined further. A Swedish RCT found that nurse-based medical titration and follow-up led to better long-term adherence than standard care amongst ACS patients.[226] Similar findings were reported in an analogous Indian RCT.[227] In a Canadian RCT amongst STEMI patients, however, an automated reminder urging long-term use of guideline-recommended medications did not improve adherence.[228] A Swedish registry study concluded that one possible explanation for worse adherence to both guidelines by physicians and to medications prescribed to ACS patients could stem from impaired renal function.[229] Moreover, a large US registry study found that a statin was prescribed less frequently to diabetic compared to nondiabetic patients upon discharge following ACS.[230] Amongst patients with chronic obstructive pulmonary disease, statins along with β-blockers and aspirin were also underutilised when compared to patients without disease. In that Danish study, a profound increase in statin use from 1995 to 2015 was generally observed.[231]

2.3 BETA BLOCKERS

Since their discovery in the 1960s, β-blockers have played a crucial role in standard medical regimens to treat both stable CAD and ACS patients. In addition, hypertension and arrhythmias alone have been treated using β-blockers for decades. For some time, they have also been used to treat heart failure patients.

2.3.1 PHARMACOLOGY

The treatment effect of β-blockers is mediated by their antiischemic, antiarrhythmic and antihypertensive properties. These properties result from the binding of a β-adrenergic antagonist to β-adrenoceptors, producing an antagonistic effect from the β-adrenergic stimuli caused by adrenalin and noradrenalin in various tissues and organs in the body. This antagonism is reversible and competitive. Thus, β-blockers both decrease the heart rate and cardiac contractility more effectively particularly when the sympathetic nervous system is activated, such as during exercise. Following an MI, β-blockers were shown to improve ventricular remodelling, prevent fatal arrhythmias and, most of all, decrease oxygen demand from the myocardium.[232]

β-blockers have been classified as (cardio-) selective and nonselective based on their binding properties to β-adrenergic receptor types 1 (mainly expressed in the heart tissue) and 2 (also expressed in, for instance, the blood vessels, gastrointestinal tract and lungs). Selective, second-generation β1-blockers have a higher affinity to the β1 receptor, since nonselective first-generation β-blockers bind to both receptors at a similar magnitude. This selectivity depends on the dosage and is lost at higher doses. Currently, cardioselective β-blockers are preferred, although nonselective β-blockers remain relevant in certain settings.[232]

β-blockers are generally well-tolerated, although they may naturally cause adverse effects particularly when used in larger doses. The most common adverse events include cardiovascular events, such as bradycardia and Raynaud's phenomenon, as well as more general effects including fatigue, headaches and insomnia and the impairement of sexual function stemming from the loss of libido or aggravating impotence. β-blockers, especially nonselective β-blockers, can also mask the symptoms of hypoglycaemia (e.g., tachycardia and tremours) amongst insulin-dependent diabetic patients. In addition, β-blockers may increase airway resistance, causing a life-threatening situation, such that asthma and bronchospastic obstructive pulmonary disease represent relative contraindications for initiating β-blockers. Absolute contraindications for β-blockers include symptomatic hypotension or bradycardia and severe decompensated heart failure.[232]

As early as the 1970s, clinicians recognised that the abrupt discontinuation of long-term β-blocker therapy may exacerbate angina, acute myocardial infarction or even sudden cardiac death.[233,234] This β-blocker withdrawal syndrome was thought to arise from a β-adrenergic hypersensitivity acquired during the long-term use of β-blockers. During long-term treatment, the number of β-adrenergic receptors expressed appeared to increase in the myocardium and, if the β-blocker was abruptly discontinued without a stepwise decrease in the dosage, the effect of adrenergic agents—for example during exercise—could overwhelm the myocardium due to the increased sensitivity to them.[235] Several studies conducted during the pre-reperfusion era showed a marked deterioration in a patient's condition,

tachycardia, a decrease in EF and blood pressure elevation amongst patients with previous CAD or heart failure when they discontinued β-blockers.[234,236] However, a study from the 1980s concluded that the withdrawal syndrome was not clinically important amongst AMI patients, whereby their β-blocker could be abruptly discontinued if indicated.[237] A more recent study suggested that the withdrawal syndrome was associated with an increased risk of MI only with cardioselective β-blockers.[238] However, given the possibility of rebound symptoms, if necessary, long-term β-blocker therapy should be gradually discontinued through a stepwise decrease in the daily dosages.

2.3.2 LONG-TERM USE OF B-BLOCKERS FOLLOWING ACS

Most studies affirming the role of continuous β-blocker therapy following MI predate routine reperfusion therapies.[239] Conclusive evidence from the reperfusion era, however, remains lacking.[21] Yet, continous β-blocker therapy is recommended in ESC guidelines for all STEMI patients irrespective of their cardiac function when no contraindications are present. As a class I recommendation with level-A evidence, β-blockers are indicated for patients with HF and/or LVEF ≤40%, whilst a class IIa recommendation with level-B evidence provides for routine β-blocker consideration for all STEMI patients.[116] For NSTE-ACS patients with preserved cardiac function, however, routine β-blocker therapy is no longer recommended.[117] Yet, the need for further studies examining β-blocker use in patients with normal or mildly lowered LV function is outlined in the guideline. For NSTE-ACS patients with LVEF under 40%, β-blockers are also recommended. Moreover, the latest US guidelines continue to recommend life-long β-blocker therapy for all post-MI patients, although amongst patients without HF or hypertension, 3 years of β-blocker therapy might be sufficient.[118,119,240] Based on previous evidence suggesting a reduction in mortality accompanying carvedilol, metoprolol, bisoprolol and nebivolol, only these agents are recommended.[22,241-246]

As the recommendations in guidelines indicate, recent observational studies have identified the most prominent association from the benefits associated with β-blockers following MI amongst high-risk patients, that is, patients with lowered LVEF, a history of prior MI or multivessel disease.[247-251] In these studies, follow-up lasted from six months to nearly four years. Furthermore, both Dondo et al. and Puymirat et al. concluded in their recent studies that MI patients without HF do not exhibit a lower mortality from long-term β-blocker therapy.[26,30] In a subgroup of previous MI patients from a large observational study, β-blocker therapy did not associate with a lower risk of composite cardiovascular events. However, other recent studies found an independent reduction in one-year mortality associated with β-blocker therapy amongst all ACS patients regardless of their risk profile.[25,32,252,253] Furthermore, a meta-analysis of STEMI patients treated with PCI identified an association between lower all-cause mortality and β-blockers amongst

patients with preserved LVEF.[27] Additionally, a recent retrospective study with propensity score matching also identified an association between β-blocker use and decreased long-term mortality in a lengthy five-year follow-up amongst ACS patients with preserved cardiac function.[31] Another observational study amongst patients with a first MI linked long-term β-blocker therapy with a lower rate of recurrent MI and all-cause mortality with a follow-up extending to at least 3.7 years.[24] Furthermore, two more recent publications, a meta-analysis and a cohort study recommended long-term β-blocker use for all ACS patients including low-risk patients, even one year following a cardiac event.[28,29] Yet, again, a recent systematic review claimed that discontinuing the β-blocker therapy one year after an MI amongst patients with preserved LV function would be reasonable if no other indications for its use existed.[33] This finding was supported by a more recent observational study amongst MI patients over 65 years old for whom no benefit was found from β-blocker use three years following an MI.[34]

Only a few RCTs have been performed in the reperfusion era on the long-term use of β-blockers. The Carvedilol Post-Infarction Survival Control in the Left-Ventricular Dysfunction (CAPRICORN) trial demonstrated that carvedilol therapy reduced both the recurrence of MI and long-term mortality amongst patients after an MI complicated by LV dysfunction.[22] Moreover, the recent Carvedilol Post-Intervention Long-Term Administration in Large-Scale Randomised Controlled Trial (CAPITAL-RCT) suggested that low-risk STEMI patients would not benefit from long-term carvedilol therapy following PCI.[23] Unfortunately, this study was evaluated as underpowered and, thus, carried a limitation in the generalisability of the findings. However, these few RCTs support the idea of a limited benefit from β-blockers for low-risk patients following an ACS event.

Still, evidence for or against the long-term use of β-blocker therapy following ACS, particularly for low-risk patients with preserved LV function, remains inconclusive. This might be one of the reasons why adherence to β-blocker therapy amongst other secondary preventive medications is quite poor. Wide variation exists in the adherence to guidelines by physicians.[254,255] Overall, adherence to β-blockers decreases with time following an ACS event.[15,228,256] High-risk patients appear to adhere to medication use more poorly, which is particularly alarming.[257] Few studies have examined the effect of adherence to secondary prevention medications on long-term survival. Hamood et al. found that nonadherence to β-blockers, as opposed to other medications, did not affect all-cause mortality amongst post-MI patients.[258] Yet, in a study of both MI and non-MI patients following CABG, inconsistent or nonuse of β-blockers increased mortality when compared to regular use.[259]

After the 1990s, examinations of β-blocker withdrawal syndrome are scarce and solid evidence from RCTs of its effect on ACS patient survival remains lacking.[260] However, the phenomenon is real and to some extent might explain worse outcomes amongst nonadherent ACS patients in some studies.

2.4 NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDS)

NSAIDs are the most commonly used painkillers worldwide. They are broadly utilised for multiple purposes because of their analgaetic, antipyretic and antiinflammatory effects.[35] However, NSAIDs are also well known for their adverse gastrointestinal and renal effects.[261,262] Their harmful effects on the cardiovascular system, including the elevation of blood pressure, fluid retention and, therefore, an increased risk of exacerbating heart failure, were also discovered long ago.[263,264] Growing evidence of unfavourable outcomes—namely, an increased risk of MI on both stable CAD and ACS patients—has emerged within recent decades as well.[36,265,266]

2.4.1 PHARMACOLOGY AND ADVERSE CARDIOVASCULAR EFFECTS

NSAIDs inhibit the cyclooxygenase (COX) enzyme, which has two different isoforms, COX-1 and COX-2. Both isoforms produce prostaglandin H2 (PGH-2) from arachinodic acid, whereby PGH-2 is, in turn, converted to prostanoids, more specifically, thromboxanes, prostacyclins and prostaglandins, by different enzymes depending on the tissue. These prostanoids mediate different bodily functions, including the protection of gastric mucosa by prostaglandin E2 (PGE-2) and prostacyclin (PGI-2) produced by COX-1. In turn, PGE-2 formed by COX-1 in the kidneys participates in the regulation of glomerular filtration, whilst COX-2- generated PGI-2 affects renin secretion amongst others. Furthermore, both COX isoenzymes produce PGI-2 in the arteries, causing vasodilation and antithrombotic effects. In turn, thromboxane A2 (TXA-2) formed by COX-1 in thrombocytes antagonises the effects of PGI-2.[267,268]

NSAIDs are classified as nonselective COX-1 and COX-2 inhibitors (acetylsalicylic acid, ibuprofen, diclofenac, ketoprofen, indomethacin and naproxen), preferential COX-2 inhibitors (meloxicam, nimesulide and etodolac) and selective COX-2 inhibitors (celecoxib, rofecoxib, etoricoxib and valdecoxib) based on their selectivity to the COX isoforms.[267,268]

The cardiovascular, or more precisely thrombotic, adverse effects of NSAIDs are thought to stem from multiple factors and vary greatly between different NSAID agents.[267-269] Whilst inhibiting COX-2 and, therefore, the formation of possibly cardioprotective PGI-2, nonselective NSAIDs also inhibit the production of thrombogenic and vasoconstricting TXA-2 by COX-1. Selective COX-2 inhibition, however, leads to the decreased concentration of vasodilating and antithrombotic PGI-2, whilst the formation of harmful

TXA-2 remains uninhibited.[270] This was the first mechanism hypothesised to increase the CV risks from selective COX-2 inhibitors, yet clearly not providing a complete explanation.[271] It seems that the overall strength of COX-2 inhibition is the primary factor contributing to the risk for the CV events from NSAIDs.[272] The decrease in PGI-2 causes a thrombogenic state, elevates blood pressure and possibly leads to atherosclerosis. Other proposed mechanisms participating in the elevated CV risk include the inhibited effect of PGI-2 towards resisting the ischemic-reperfusion injury to the myocardium and the inhibition of the cardioprotective effects from statins.[273-276] Overall, however, the precise mechanisms of the cardiovascular adverse effects remain unknown.

2.4.2 LONG-TERM RISKS AMONGST ACS PATIENTS

Previously, the antiinflammatory and analgetic effects were assumed to be mediated only by the COX-2 isoenzyme, whilst COX-1 inhibition would lead to adverse gastric effects (a bleeding or perforated gastric ulcer representing the most serious). This led to the development of COX-2 selective NSAIDs, namely, coxibs. Several RCTs demonstrated the more favourable gastric properties of coxibs, whilst surprisingly and simultaneously discovering the increased risk of thrombotic events associated with their use, specifically with rofecoxib.[37-41] This discovery also emerged in observational studies.[36] In 2004, rofecoxib was voluntarily withdrawn from the US market because of the increased cardiovascular risks. In 2005, the European Medicines Agency contraindicated the use of coxibs in patients with ischemic heart disease.[42] Then, in 2007, a focused update from AHA discouraged the use of all NSAIDs in CAD patients.[43] Since then, evidence has increasingly mounted. Today, amongst COX-2-selective NSAIDs, only celecoxib is available in the US, whilst in Finland etoricoxib is also prescribed. Recently, celecoxib was repeatedly proposed as noninferior compared to nonselective ibuprofen or naproxen regarding its CV safety profile.[277-282] However, recent review articles thoroughly highlighted the limitations of celecoxib RCTs (SCOT and PRECISION), concluding that celecoxib's safety over nonselective NSAIDs is far from established.[268,283] In addition, recent observational studies have also summarised similar findings.[284]

Recent studies associated NSAID use not only with a greater risk of both first-time and recurrent MI, but also with increased coronary, cardiovascular and all-cause mortality. [45,46,48,285-289] For MI patients, the risk of increased mortality appears to persist for several years following a cardiac event whereby not even the short-term use of NSAIDs is recommended.[46,47] Moreover, using NSAIDs was also recently associated with an increased risk for stroke and atrial fibrillation.[290,291] Given their mechanism of action, NSAIDs are thought to mediate their adverse effects on coronary patients through thrombotic complications. However, NSAIDs also increase the risk for bleeding, possibly

aggravated specifically amongst post-ACS patients receiving antiplatelet or anticoagulant therapies.[48,292,293] Previous studies indicate that no NSAID irrespective of their selectivity is safe for CAD patients.[47,286] Based on the available evidence, in addition to patients with established CAD, guidelines already recommend avoiding all NSAID use amongst those patients at an elevated risk for cardiovascular disease.[117-119,275] Yet, despite clear evidence against them, NSAIDs remain quite commonly prescribed to and used by ACS and CAD patients.[35,43,44,46,289,294]

2.5 RED BLOOD CELL (RBC) TRANSFUSION

2.5.1 ANAEMIA AND BLEEDING AMONGST ACS PATIENTS

Besides evaluating the risk of ischemic complications during acute treatment for ACS patients, risk assessment includes considering bleeding risk as well. Primarily stemming from highly effective antithrombotic therapy, anticoagulation and procedures performed (PCI and CABG), ACS patients are at greater risk of bleeding.[9,10] Individual characteristics, such as an advanced age, female gender, renal insufficiency, hypertension and a history of previous bleeding, associate with an increased risk of major bleeding during an ACS event.[295] To estimate the bleeding risk for an ACS patient, few risk scores have been developed.[296,297] Due to their heterogeneity and lack of validation for any of the scores, a new definition for high bleeding risk was recently published by the Academic Research Consortium for High Bleeding Risk (ARC-HBR), which focuses on the risk assessment of patients undergoing PCI, whether in an acute setting or not.[298]

Heterogeneous definitions of major bleeding has also been applied, partly explaining why the incidence of major bleeding complications varied greatly amongst ACS patients in prior studies, ranging from <1% to around 10%.[10,299-302] Moreover, the proportion of patients requiring RBC transfusions also varied from 4% to 30%.[303] A position paper by ESC described several tools to define bleeding events: the Thrombolysis in Myocardial Infarction (TIMI) and the Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) representing the most commonly used tools.[304,305] Yet, to systematise both clinical use and reporting bleeding events in clinical trials using a validated method, the Bleeding Academic Research Consortium (BARC) definition of bleeding was developed.[306,307]

Major bleeding has been independently associated with increased adverse outcomes (including recurrent MI, stent thrombosis and stroke), specifically with both short- and long-term mortality amongst ACS patients.[10,295,301,308-313] Several possible reasons explain this increased mortality caused by bleeding. In addition to possible ischemia caused by a lower blood volume and a reduction in oxygen delivery, the discontinuation of antithrombotic therapies

followed by the accretion of new thrombus in the coronary artery serves as one possible explanation.[314,315] However, discontinuing antithormbotic therapy is recommended if bleeding leads to hypotension or is life-threatening.[306]

Anaemia, defined by the World Health Organisation (WHO), occurs with a haemoglobin (Hb) concentration under 130 g/l in men and under 120 g/l in women.[316] Even without bleeding, 10% to 43% of ACS patients are already anaemic at baseline.[317] Independent of comorbidities, anaemia was repeatedly found to directly associate with an increased short- and long-term mortality amongst ACS patients.[318-322] This relationship is most likely multifactorial, but one probable explanation is exacerbated myocardial ischemia, likely caused by decreased blood oxygen levels and increased myocardial oxygen demand due to a reactive increase in cardiac output.[321]

2.5.2 RBC TRANSFUSIONS FOR ACS PATIENTS

Both anaemia and bleeding have been treated for decades using RBC transfusion to replenish both the circulating blood volume and its oxygenative capabilities, eventually thought to minimise myocardial ischemia.[11] However, in recent decades, an independent association between RBC transfusion and poorer outcomes both in general use and amongst ACS patients was found. Guidelines already recommend a restrictive (Hb target >80 or 70g/l) over liberal (Hb target >100g/l) transfusion strategy to all other patient subgroups, including stable CAD patients, except ACS patients.[13,14,323]

Recent studies amongst ACS patients demonstrated somewhat controversial results on this topic. Only a few RCTs exist, with contradictory results. For instance, Cooper et al. concluded in their RCT that a liberal versus restrictive transfusion strategy associated with a poorer outcome amongst ACS patients.[324] Yet, Carson et al. argued that a liberal strategy could even decrease mortality when compared to a restrictive strategy.[325,326] However, RCTs conducted on critically ill patients in noncardiac settings linked a restrictive strategy to a better or at least similar survival compared to a liberal strategy.[327-330] Yet, in an RCT comparing a liberal to restrictive transfusion strategy following hip replacement surgery amongst patients at high CV-risk a liberal strategy did not affect long-term mortality.[331]

Registry studies quite conclusively associated RBC transfusion or the liberal transfusion strategy with an increased mortality amongst ACS patients. This association was found for short-term in-hospital mortality for up to one-year.[303,332-336] Yet, the impact on long-term survival remains unclear. In some studies, however, RBC transfusion associated with either a neutral or even beneficial outcome related to in-hospital mortality.[337,338] In a small retrospective study of non-ACS patients with a myocardial injury (diagnosed with troponin release), avoiding blood transfusion for patients with Hb <80 g/l associated with a poorer outcome.[339] In addition to mortality, RBC

transfusion associated with an increased risk for both adverse cardiac events and stroke following cardiovascular interventions.[340,341]

A recent meta-analysis of observational studies from 1966 to 2016 strenghtened the association of increased mortality and reinfarction rates with RBC transfusion therapy amongst ACS patients.[342] Transfusion seemed beneficial or at least neutral amongst patients with Hb <80g/l, but detrimental amongst patients with Hb >100 g/l. Similar results were observed amongst elderly MI patients in a recent French study.[343] In addition, a meta-analysis consisting of STEMI patients concluded that RBC transfusion increases mortality and morbidity amongst these patients, whereby the observed difference cannot be explained by comorbidities alone.[344] Another rigorous meta-analysis conducted by Chatterjee et al. also demonstrated that RBC transfusion or a liberal strategy independently associated with an increase in all-cause mortality.[345] However, aside from the one RCT (Cooper et al.) mentioned, this meta-analysis relied on observational studies, where both a bias in the association between the indication (anaemia or bleeding) and treatment as well as a bias from unmeasured confounding factors persisted.[346,347]

Due to this inconclusice evidence, guidelines have remained unable to determine best practice regarding RBC transfusion for anaemic or bleeding ACS patients.[12] Yet, caution is recommended when treating ACS patients with transfusions. Based on the best available evidence, using RBC transfusion is justified when Hb <80 g/l and avoided when Hb >100g/l.[317] Within that gray area, however, decisions must be made on a case-by-case manner. Moreover, preventive measures should be considered in order to minimise the risk of bleeding.[308,348] This can be achieved by, for example, identifying vulnerable patients using risk assessment tools, reducing the dosage of antithrombotic agents and using radial instead of femoral access in coronary interventions.[297,349-351] Since nonaccess-site bleeding associates with an even greater risk for adverse outcomes compared to access-site bleeding, the importance of other strategies to minimise bleeding, irrespective of the route of access, cannot be sufficiently emphasised.[352,353]

3 AIMS OF THE STUDY

The primary aim of this study involved filling the gaps in our knowledge related to factors contributing to ACS patients' long-term survival. More precisely, we aimed to identify medical behaviour and its effect on ACS patients' survival and to study the effect of transfusions given in an acute setting on ACS patients' long-term prognosis. The objectives of the four studies were as follows:

1) To determine the utilisation rate of statins following an ACS event at Helsinki University Central Hospital (HUS) and to assess the effect of adherence to statins on ACS patients' long-term mortality.

2) To assess the effect of RBC transfusion administered during acute treatment on the long-term morbidity and mortality of ACS patients.

3) To determine prescription filling and adherence rates to β-blockers following ACS and to examine the effect of nonadherence to β-blockers on ACS patients' long-term survival.

4) To elucidate the usage rate of prescribed NSAIDs and the effect of current NSAID use on the risk of recurrent MI and death amongst ACS patients.

4 METHODS

4.1 STUDY COHORT

Between March 2006 and March 2008, all consecutive patients undergoing an angiography (n = 5809) at Helsinki University Central Hospital (HUS) were assessed for inclusion in the Genetic Predisposition of Coronary Artery Disease (COROGENE) study protocol. After exclusions due to a low haemoglobin or recent blood transfusion, prior heart transplant, non-Finnish citizenship or recurrent angiography for patients already in the cohort, 5294 patients (91.1%) were ultimately included in the study. Amongst these, 2090 (39.5%) patients were primarily diagnosed with ACS. The ACS diagnosis was based on an episode of typical chest pain associated with cardiac ischemia, an elevated biomarker measured from the patient's blood sample (TnT and CKMBm at the time of cohort inclusion) and typical ischemic changes in ECG. Furthermore, to verify the diagnoses, at least one significant >50% stenotic lesion had to be identified in a coronary angiography. Studies I through IV of this thesis are based on this cohort of ACS patients from the COROGENE study. All patients were treated using the standard procedures and medical regimens characteristic for that time period.

The COROGENE registry was collected from comprehensive medical records and from a two-page questionnaire patients completed during hospitalisation. The registry included information on the patient's medical history, comorbidities, physical measurements such as height and weight, prior cardiovascular procedures, cardiovascular risk factors including smoking habits, information on the patient's relatives, admission and discharge medications, angiography results, information on the revascularisation method (thrombolysis, PCI and CABG), laboratory samples, ECG findings and the patient's current condition.

All patients provided their written informed consent. The Ethics Committee of HUS approved the research protocol for the COROGENE study. This study also complies with the 1964 Declaration of Helsinki and its subsequent revisions.

4.2 DATASETS

In addition to the COROGENE registry, we merged different national datasets used in the studies at the patient level using each patient's unique social security number. To assess drug usage and adherence to secondary prevention medications, information on filling prescriptions was collected from the Social Insurance Institution of Finland (SII). The Finnish Prescription Register from

the closed pharmacy system covers all prescription medication purchases, from which information beginning 1 January 2005 was acquired. For the statins in study I, medical follow-up lasted until March 2009. For the β-blocker and NSAID studies III and IV, data were updated to cover purchases until the end of the 2015. Data include information on filled prescriptions as follows: the date the prescription was filled, the anatomical therapeutic chemical (ATC) code of the drug, the strength of the medication (i.e., amount in grams or milligrams), the package tablet count and the number of packages reclaimed. Unfortunately, neither the indication for use nor the dosage prescribed was provided.

To investigate the incidence of comorbidities, such as heart failure and cancer as well as the recurrence of cardiac events and other rehospitalisations, data on hospital discharge diagnoses and readmissions were aquired from the Finnish Institute for Health and Welfare. The Care Register for Health Care (HILMO) includes information on admission and discharge dates as well as the primary and secondary diagnoses for every hospitalisation in Finland. The follow-up period for these data began in January 2006 for studies II through IV and extended until December 2014 and December 2015, respectively, for studies II and studies III and IV.

Information on causes of death and mortality were obtained from Statistics Finland, and follow-up lasted until the patient's death or the end of the follow-up period, whichever occurred first. The follow-up period lasted until 31 March 2009 in study I and 31 December 2015 for studies II through IV.

To analyse the number, frequency and type of blood transfusions given during the acute treatment of ACS patients, data on transfusions and haemoglobin values were obtained from the comprehensive hospital transfusion registry of HUS. These data consisted of information on the type and units of blood product(s) administered, the transfusion date and all measured haemoglobin values in HUS laboratories during the assessment period. Data covered all transfusions administered from January 2005 until October 2014.

4.3 PATIENT SELECTION AND DEFINITIONS

Table 2 summaries patient selection, exclusion criteria and final study populations, along with further details such as the follow-up periods and outcomes.

4.3.1 ADHERENCE TO STATINS (STUDY I)

In this study, all statin agents (ATC codes C10AA) were analysed as a single pooled-medication group. The methods to assess adherence to statins relied on the timing of the first refill following discharge, the number of refills and

the time intervals between them. In Finland, patients are reimbursed for prescription refills extending beyond a maximum of 3 months or 100 days.

We assessed both primary and secondary adherence to statins following an ACS event. For secondary adherence, we divided patients into three statin user groups: regular users, irregular users and nonusers. If no prescriptions were filled during follow-up or after only one was filled more than 180 days until a patient's death or until the end of the follow-up period, the patient was categorised as a nonuser. Patients who filled a prescription within 30 days after discharge followed by at least one refill with no intervals greater than 180 days between refills were categorised as regular users. If neither of the aforementioned criteria were satified, the patient was categorised as an irregular statin user. To ensure that the results were not sensitive to our use of 180 days as the cut-off for a permitted interval, we performed sensitivity analyses with refill intervals of 90, 120 and 150 days. To assess the utilisation of statins further, we examined the overall duration of statin use by calculating the time from the first to the last refill and adding 90 days to that time (50% of the assumed refill period). The overall duration was then divided by the total number of refills to calculate the mean interval between them. Regular statin users were further subdivided into groups based on the mean refill intervals of 100 days or less versus more than 100 days, derived from the maximum reimbursement time (3 months) for a single refill in Finland.

Primary adherence refers to how well patients adhere to the initiation of a new medication. Therefore, for these analyses, we excluded patients already taking statins prior to hospitalisation (n = 780). In total, we examined 1099 statin-naïve patients, dividing them into three categories based on the timing of their first prescription fill following discharge: within 7 days, 7 to 120 days, after 120 days or no filling at all.

4.3.2 RBC TRANSFUSION (STUDY II)

In this substudy, 85 previously transfusion-naïve non-CABG patients treated with at least 1 RBC transfusion unit during hospitalisation were compared to 1278 nontransfused patients. Due to the substantial discrepancy in both the size and characteristics of these two groups, we calculated the propensity score for RBC transfusion treatment using logistic regression. In the regression analyses, we included all baseline variables with a significant difference between groups applying $p < 0.05$. Using the propensity score, we then matched in a 1:1 fashion 65 patients to each group to mitigate any confounding from the significant differences between them. We assessed the adequacy of matching using c-statistics and the covariate balance applying the Hosmer–Lemeshow goodness-of-fit test. The propensity score itself was eventually included as a covariate in the final multivariable models. To further verify findings adjusting for confounding and inflating the cohort size, we further

performed inverse propability treatment weighted (IPTW) Cox regression analyses after propensity matching.

We obtained patients' haemoglobin values from HUS laboratories and evaluated them at different time points during hospitalisation and follow-up. Hb levels were compared between transfused and nontransfused patients. Due to the strong correlations between nadir–Hb levels under 100g/l (Cramer's V: 0.789, $p < 0.001$) and 80g/l (Cramer's V: 0.447, $p < 0.001$) and RBC treatment during hospitalisation, we could not include nadir–Hb in the multivariable models. However, to address any confounding from low haemoglobin levels, anaemia (based on the WHO definition described above) at baseline was used as a suitable candidate confounder in both the logistic regression for the propensity scoring as well as in the final multivariable models. In addition, RBC-transfused patients with a nadir–Hb over 80g/l were compared to patients with a nadir–Hb below 80g/l. Furthermore, subgroup analyses of anaemic and nonanaemic patients were performed to determine what more prominently influenced mortality between RBC transfusion and anaemia.

4.3.3 ADHERENCE TO β-BLOCKERS (STUDY III)

In study III, we assessed the utilisation of prescribed [excluding over-the-counter (OTC) aspirin] secondary prevention medications in pooled pharmacological groups. Pooled groups were formed using the anatomical therapeutic chemical (ATC) codes; β-blockers (ATC: C07), statins (ATC: C10AA and C10BA) and renin-angiotensin-aldosteron (RAA) inhibitors consisting of angiotensin-converting enzyme (ACE) inhibitors together with angiotensin receptor blockers (ARB) (ATC: C09). The preferred ADP inhibitor by the time of our cohort recruit, clopidogrel, was pooled with newer antiplatelet medications (ATC: B01AC04–05, 07, 22, 24 and 30) and their usage was examined only for the first 12 months following discharge.

Adherence to each pooled medication group was assessed on an annual basis separately and the adherence status of each year was then introduced to the survival analyses as a time-dependent variable. To define annual adherence, the follow-up time was split into periods of 365 days, beginning from the discharge date and ending at patient's death or at the end of the follow-up period. A specific yearly period was categorised as adherent if the patient filled the presctiption ≥3 times during the year and 180 days or more elapsed from the first through the last refill. In previous studies, this method was associated with an 80% adherence rate, typically the cut-off for good adherence.[354,355] For a death during the assessment period, the patient was also considered adherent if one of the following conditions was satisifed:

1. The patient filled 1 to 2 presciptions during the period and the time from the last refill until death did not exceed 100 days.

2. The patient recorded zero refills during the period, although the preceding period featured adherence and the interval between the last refill and both the beginning of the next period and the patient's death did not exceed 100 days.

If neither of these criteria were met, the yearly period was defined as nonadherent. The 100-day interval stems from the maximum reimbursement time for Finnish pharmaceuticals. As sensitivity measures, we also assessed intervals of 90 and 120 days. Furthermore, for sensitivity, adherence was also examined as a three-category variable based on the number of annual refills: poor (0–1 refills), intermediate (2 refills) and good (3 or more refills).

This study focused on β-blockers, such that the usage of other drugs was primarily assessed as a confounding factor. However, adherence to each of the secondary prevention medications was assessed separately. Furthermore, the association between survival and adherence to each medication was examined in univariable models by excluding patients without a prescription to the drug in question.

In the multivariable models, however, only the effect of adherence specifically to β-blockers on survival was analysed, whilst adjusting for the concomitant usage of other drugs. Hence, only patients prescribed β-blockers upon discharge were included in these multivariable analyses. Adherence and its effect on survival was also examined in low-risk and high-risk patient subgroups.[356,357] A patient was regarded as high risk if they suffered a prior MI, was diagnosed with HF (HILMO) at baseline or was diagnosed with triple vessel disease in CAG. Otherwise, patients were considered low risk.

4.3.4 NSAID USE

In contrast to secondary prevention medications, ACS patients should avoid using NSAIDs. Therefore, methods to examine the utilisation of these drugs also differed from previous studies. To estimate changes in prescribed NSAID-use behaviour across years, follow-up was again divided into yearly periods and the number of NSAID prescription fills for each annual period was determined. For the utilisation analyses, we identified the number and percentage of patients filling at least one or at least three NSAID prescriptions per year. We then assessed these annual utilisation rates throughout the follow-up period.

Prior studies found that the adverse effects of NSAIDs may both appear and vanish quite rapidly after the initiation and discontinuation, respectively, of administering a medication.[47,285,358] To assess the association of recent or current NSAID use with patient death or recurrent MI, we identified the nearest NSAID refill before an outcome event. The days' supply for this refill was estimated using information on the tablet count from a purchase (SII registry) combined with a defined daily dose (DDD) provided by WHO for each medical agent.[359] Patients were then categorised as current NSAID users and

nonusers for a comparison. If the days' supply of the most-recent refill lasted at least until 30 days before the event, the patient was defined as a current user. If there were no NSAID prescription fills or the days' supply ended more than 30 days before the outcome, the patient was considered a nonuser. For the sensitivity measures, user definitions based on half the DDD as well as a doubled DDD were also examined. Furthermore, we also assessed usage defined in the same manner using a 60-days cutoff for the days' supply before the event.

The concomitant use of secondary prevention medications was adjusted by assessing their usage in a similar days' supply method based on DDDs and tablet counts. The medication groups formed using the ATC codes were identical to study III. Using different NSAID agents, their proportional usage was calculated; yet, given the low number of NSAID refills, all NSAID agents were assessed as one pooled medication group (ATC: M01A).

To further investigate NSAID usage and its effect on ACS patient prognosis, we divided the study population into high- and low-risk patient subgroups, defined in manner similar to that in study III.

4.4 STATISTICAL METHODS

All statistical analyses were performed using IBM's SPSS software, versions from 18.0 to 24.0 (SPSS, Inc., Chicago, IL, USA). We considered $p < 0.05$ as statistically significance using two-tailed tests. Across all studies, we compared baseline characteristics and other variables between defined groups. We used cross-tabulations to analyse categorical variables and the differences were tested using either chi-square or the Fisher's exact test, whichever was appropriate for the specific variable. Values are stated as percentages, with continuous variables presented as either a median with an interquartile range (IQR) or a mean with the standard deviation (SD) depending upon the suitability. We assessed the normality of distribution for continuous variables graphically and using the Kolmogorov–Smirnov test. If normally distributed, we analysed continuous variables using an independent samples t-test; nonparametric tests, namely, the Mann–Whitney U, were applied to nonnormally distributed variables.

In studies I through III, univariable comparisons of the mean survival times for each variable were analysed using the Kaplan–Meier survival analysis, whereby the associations for each candidate confounding variable and its impact on survival was also assessed using a univariable Cox proportional hazards model. For these, hazard ratios (HRs) with 95% confidence intervals (CIs) are presented. The final multivariable Cox proportional hazards models were constructed from candidate variables based

on their clinical relevance from prior studies as well as based on their statistical significance on outcomes in univariable models.

In studies I and II, variables were entered into the Cox regression models with both forward and backward stepwise variable-reduction methods to form the final equations. In studies III and IV, the introduction of covariates to the multivariable models were carried out using the enter method. For the Cox regression models, the assumption regarding proportional hazards was tested through a visual comparison of the Kaplan–Meier curves as well as by plotting the Schoenfeld's residuals against survival time. We observed no violations. The multicollinearity, in turn, was examined using variation inflation factors (VIFs) between independent variables. No deviations with a value >2.5, considered the significant threshold of collinearity, were observed. In study III, the incidence of HF during the follow-up, usage of other secondary prevention medications and adherence to β-blockers were analysed as time-dependent variables in the Cox proportional hazards models. HRs with 95% CIs are reported. In study II, in addition to the regular Cox regressions models before and after matching, an IPTW Cox proportional hazards model was also calculated following propensity score matching.

In study IV, given the nature of the method used to assess current NSAID use, logistic regression was utilised to both examine the effect of each candidate variable on the composite endpoint of mortality and recurrent MI in univariable models as well as to calculate the final multivariable models. Results are reported in odds ratios (ORs) with the corresponding 95% CIs. A VIF value of 2.5 was again considered the significant thresfold for multicollinearity, which was not encountered.

Table 2. ***Materials and methods used in studies I through IV.*** *Abbreviations: CABG, coroary artery bybass grafting; CAG, coronary angiography; CV, cardiovascular; HF, heart failure; HILMO, Care Register for Health Care; HUS, Hospital District of Helsinki and Uusimaa; IPTW, inverse probability treatment weighting; MI, myocardial infarction; NS, nonsignificant; NSAID, nonsteroidal antiinflammatory drug; RBC, red blood cell; SII, Finnish Prescription Register of Social Insurance Institution of Finland; TF, transfusion.*

	Study I	**Study II**	**Study III**	**Study IV**
Complete required data	n = 2018	n = 2009	n = 2009	n = 2009
Exclusions	30-d discharge mortality[i] n = 73	TF prior hospitalisation n = 64 First TF after hospitalisation n = 289 Only TF other than RBC n = 4 CABG[ii] n = 243 30-d discharge mortality n = 46	NS (<50%) stenosis in CAG n = 88 30-d CAG mortality[iii] n = 66	NS (<50%) stenosis in CAG n = 24 30-d CAG mortality n = 66
Final study population	**n = 1945** Regular user (n = 1200) Irregular user (n = 651) Nonuser (n = 94)	**n = 1363** RBC transfusion (n = 85) No transfusion (n = 1278)	**n = 1855** Survivors (n = 1297) Deceased (n = 558)	**n =1919** Current NSAID users (n = 88) Nonusers (n = 1831)
Subgroups	Regular users' mean interval: ≤100 d (n = 1036) >100 d (n = 164)	After 1:1 matching n = 65 vs n = 65	High-risk (n = 783) Low-risk (n = 1072)	High-risk (n = 797) Low-risk (n = 1122)
End of follow-up	31 March 2009	31 December 2015	31 December 2015	31 December 2015

	Study I	Study II	Study III	Study IV
Median follow-up	23 months (IQR 11 months)	8.6 years (95% CI 8.59–8.68)	8.6 years (95% CI 8.60–8.69)	8.7 years (95% CI 8.64–8.74)
Additional data used	SII	HILMO, TF registry of HUS	SII, HILMO	SII, HILMO
Multivariable regressions	Cox proportional hazards	Cox proportional hazards Propensity score (logistic regression) IPTW	Time-dependent Cox proportional hazards	Logistic regression
Outcomes	1. **All-cause mortality**	1. **All-cause mortality** 2. **Cancer incidence** (ICD-10 codes C) 3. **Cancer mortality** (ICD-10 codes C)	1. **All-cause mortality** 2. **Coronary mortality** (ICD-10 codes I20-I25) 3. **Recurrent hospitalisations** a. CV reasons (I20.0, I21–I22, I61, I63 and I64) b. HF (I42 and I50) c. MI (I21–I22) d. Non-CV reasons (all except CV codes)	1. **Composite endpoint** Rehospitalisation for **recurrent MI** (I21–I22) and **all-cause mortality**

i In-hospital mortality and mortality up to 30 days after discharge.
ii CABG patients excluded because of the high correlation with RBC transfusion (Cramer's V: 0.715, $p < 0.001$).
iii Mortality up to 30 days after the index angiography.

5 RESULTS

5.1 CHARACTERISTICS OF THE STUDY COHORT

The final cohorts in studies I through IV differed slightly from each other due to the exclusion criteria mentioned previously. A comparison in the general characteristics of patients from the specific substudy groups can be found in the attached original publications for studies I through III, and in the manuscript for study IV. Table 3, however, summarises these characteristics amongst both deceased and surviving patients from study III

Table 3. ***Characteristics of surviving and deceased patients in study III.*** *Abbreviations: ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; eGFR, estimated glomerular filtration; HILMO, Care Register for Health Care; IQR, interquartile range; SD, standard deviation. Adapted from Allonen et al. (2020), reprinted with permission from Taylor & Francis Group.*[360]

	Survivors (n = 1297)	**Deceased** (n = 558)	**p value**
Demographic characteristics			
Age in years, median (IQR)	62.6 (16.0)	74.4 (14.5)	<0.001
Age >65 years, %	43.3	79.4	<0.001
Female, %	26.6	37.8	<0.001
Body mass index, kg/m², mean ± SD	26.9 (±5.4)	26.3 (±5.0)	0.003
Smoker/ex-smoker, %	65.7	60.7	0.041
Comorbidities, %			
Diabetes	18.8	33.5	<0.001
Hypertension	62.4	72.8	<0.001
Kidney disease	1.0	5.4	<0.001
eGFR >60 ml/min/1.73 m², %	91.3	69.9	<0.001
Peripheral artery disease	6.5	16.5	<0.001
Atrial fibrillation	5.0	19.5	<0.001
Cerebrovascular disease	9.3	17.5	<0.001
Prior myocardial infarction	15.4	33.3	<0.001
Cardiac insufficiency at baseline (HILMO)	4.3	22.8	<0.001
Baseline anaemia	23.5	48.9	<0.001
Malignancy	5.8	12.9	<0.001
Prior procedures, %			
Coronary artery bypass graft surgery	7.2	16.1	<0.001
Percutaneous coronary intervention	9.6	14.3	0.003

	Survivors (n = 1297)	**Deceased** (n = 558)	**p value**
Vascular operation: lower extremity	2.0	6.7	<0.001
Characteristics of ACS, %			
Triple vessel disease	18.7	40.0	<0.001
Unstable angina pectoris	11.5	10.0	0.360
Non-ST-elevation myocardial infarction	50.5	63.6	<0.001
ST-elevation myocardial infarction	38.0	26.3	<0.001
Procedures, %			
Percutaneous coronary intervention	77.5	61.5	<0.001
Coronary artery bypass graft surgery	13.4	17.9	0.012
Thrombolysis	13.7	5.9	<0.001
Red blood cell transfusion during hospitalisation	13.0	22.6	<0.001
Discharge medications, %			
β-blocker	91.6	91.0	0.682
Statin	97.2	91.2	<0.001
Clopidogrel	84.0	70.3	<0.001
ACE inhibitor	59.4	54.6	0.054
Angiotensin receptor blocker	14.7	16.4	0.336
Acetylsalicylic acid	94.2	88.4	<0.001
Calcium channel blocker	9.7	20.0	<0.001
Digoxin	0.9	5.8	<0.001
Diuretic	17.9	45.1	<0.001
Nitrate	13.0	32.1	<0.001
Warfarin	3.7	14.8	<0.001
Low molecular weight heparin	12.5	23.0	<0.001
Insulin	6.8	15.7	<0.001
Oral diabetic medications	10.4	16.0	0.001
Nonsteroidal antiinflammatory drugs	6.9	13.2	<0.001
Adherence to medications, 1st year, %			
β-blocker	88.7	82.4	<0.001
Statins	88.4	80.4	<0.001
ACE inhibitor / angiotensin receptor blocker	89.8	79.8	<0.001
Clopidogrel	85.6	71.9	<0.001
Adherence to medications, 8th year, %			
β-blocker	73.0	52.7	<0.001
Statins	67.6	43.0	<0.001
ACE inhibitor / angiotensin receptor blocker	74.0	47.4	<0.001

5.2 UTILISATION OF MEDICATIONS

5.2.1 ADHERENCE TO STATINS (STUDY I)

In study I, a statin was prescribed to 95% (n = 1878/1969) of discharged patients and 90.5% (n = 1761/1945) of patients still living one month after initiating or continuing their statin therapy. In total, 58.5% (n = 1099/1969) were statin-naïve upon discharge, amongst whom 79.9% (n = 878) filled the prescription within 7 days following discharge and with another 13.1% (n = 144) did so within 7 to 120 days. A total of 77 (7.0%) patients did not fill the statin prescription at all and were, thus, primarily nonadherent. Those who filled the prescription within one week were eventually more likely to be regular statin users and less likely to be irregular statin users than those who filled the prescription within the first 4 months (regular users: 76.5% vs. 49.3%, $p < 0.001$ and irregular users: 21.5% vs. 49.3%, $p < 0.001$, respectively).

We also found that 62.0% (n = 1205) and 59.4% (n = 1155) regularly used a statin without a single refill interval of more than 180 days at the 1- and 2-year time points following discharge. Using the definition outlined previously, 61.7% (n = 1200/1945) of patients were identified as regular statin users throughout their follow-up, whilst 33.5% (n = 651/1945) and 4.8% (n = 94/1945) were irregular users and nonusers, respectively. Amongt 86.3% (n = 1036/1200) of the regular users, the mean time interval between refills was 100 days or less, whilst 13.7% (n = 164) requested fills after more than 100 days. In the sensitivity analysis for statin use, only 1.7% (n = 33), 32.2% (n = 627) and 51.6% (n = 1004) were defined as regular users using a cut-off for the interval of 90, 120 or 150 days, respectively.

5.2.2 ADHERENCE TO β-BLOCKERS (STUDY III)

In study III, adherence to secondary prevention medications was assessed separately for each year following discharge. We found that 91% (n = 1693) of patients who were still living 30 days following angiography were prescribed β-blockers upon discharge. Respectively, 95% (n = 1770), 72% (n = 1335) and 80% (n = 1480) were prescribed statins, RAA inhibitors and clopidogrel. The adherence rates to these medications for the first year were 86.8% (n = 1470/1693) for β-blockers, 86.1% (n = 1524/1770) for statins, 86.9% (n = 1160/1335) for RAA inhibitors and 82.0% (n = 1215/1480) for clopidogrel. The adherence rates decreased each year as time passed from the ACS event, and for β-blockers diminished to 71.3% (n = 926/1299) by the eighth year of follow-up, to 72.0% (n = 739/1027) for RAA inhibitors and to as low as 65.5% (n = 901/1375) for statins.

5.2.3 NSAID USE (STUDY IV)

17.7% of patients filled at least one NSAID prescription during the first year following discharge. A peak in yearly NSAID utilisation was observed during the second year of follow-up, after which the utilisation rate slightly decreased annually (Figure 3).

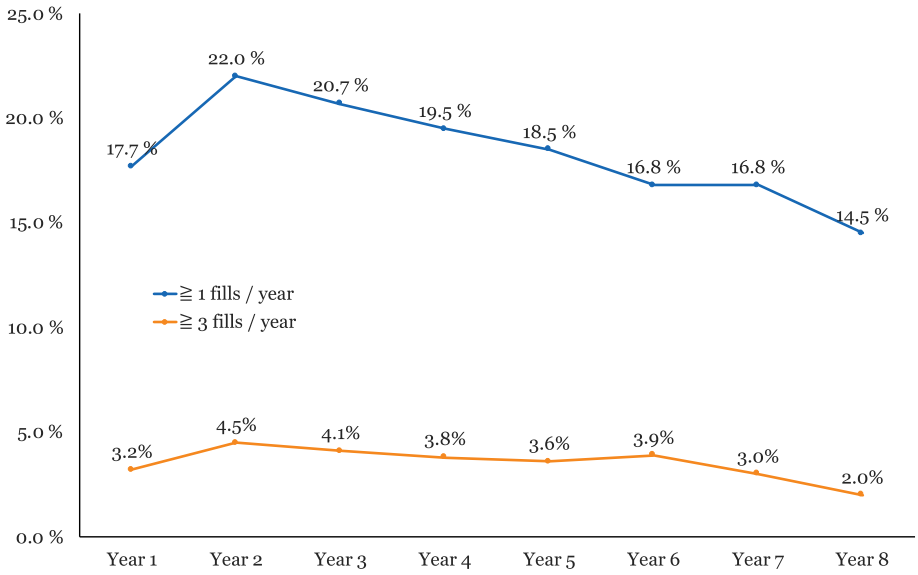

Figure 3 **Annual NSAID usage rates during follow-up.**

As many as 54.3% (n = 1042/1919) of patients filled at least one NSAID prescription during the entire follow-up period. Furthermore, 14.5% (n = 278/1919) of patients filled 3 or more NSAID prescriptions during at least one of the yearly time periods during follow-up. However, ultimately only 88 (4.6%) patients were defined as current NSAID users before the outcome event. The mean days' supply remaining at the event was 18.8 days (SD ± 36.9 days). Ibuprofen was the most common NSAID agent used amongst current users (Figure 4). Current NSAID users were compared to nonusers, and were more often treated with PCI, less frequently with CABG and did not have HF and anaemia at baseline as often as nonusers. Otherwise, the groups were quite comparable.

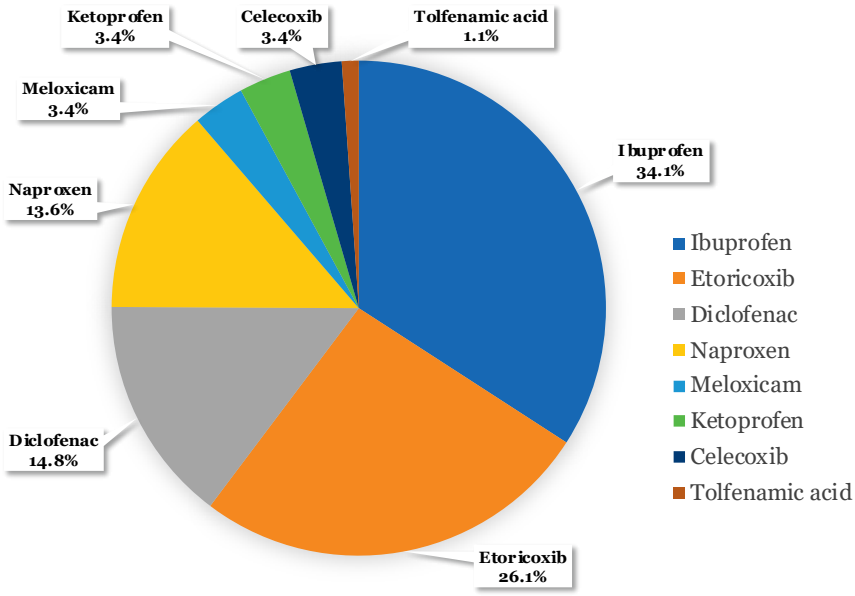

Figure 4 **The proportion of different NSAID agents amongst current users' last filled prescriptions.**

5.3 THE EFFECT OF MEDICATION USE ON PROGNOSIS

Although not entirely comparable given the different methods used in the substudies, the final multivariable risk ratios for the corresponding primary outcome for each of the primary medication groups we examined appear in Table 4.

Table 4. ***Adjusted multivariable risk ratios for the primary outcomes in studies I, III and IV.*** *Abbreviations: CI, confidence interval; HR, hazard ratio; NA, nonadherence; OR, odds ratio; TD, time dependent.*

	NA to statins (study I)	NA to β-blockers (study III)	Current NSAID use (study IV)
Regression	Cox regression	TD Cox regression	Logistic regression
Outcome	Mortality	Mortality	Mortality + Recurrent MI
HR / OR	**2.70** (95% CI 1.49–4.90) p = 0.001	**1.84** (95% CI 1.51–2.24) p < 0.001	**1.75** (95% CI 1.10–2.78) p = 0.019

5.3.1 STATINS (STUDY I)

The most strictly adherent patients primarily refilling the statin prescription within 7 days following hospitalisation exhibited a markedly lower all-cause mortality compared with patients refilling the prescription within the first 120 days (3.2% vs. 10.4%, p < 0.001). Less consistent primary adherence was associated with an increased relative risk of mortality in an adjusted Cox proportional hazards model [HR 2.34 (95%CI 1.19–4.59), p = 0.013].

Furthermore, the better the secondary adherence to statins, the lower the all-cause mortality [4.9% for regular users, 9.4% for irregular users and 14.9% for nonusers (p < 0.001)] as well as for CV mortality (2.9%, 5.1% and 7.4%, respectively, p = 0.013). We identified a stepwise increase in mortality by adherence status in a multivariable Cox model adjusted for age, ACS type, triple vessel disease, DM, cerebrovascular disease and a previous malignancy [irregular users: HR 1.53 (95%CI 1.06–2.21), p = 0.023; nonusers: HR 2.70 (95%CI 1.49–4.90), p = 0.001) compared to regular users]. In addition, amongst regular statin users, a mean interval between refills of more than 100 days also associated with a higher mortality compared to those regular statin users with a mean interval of fewer than 100 days [11.0% vs. 4.0%, p < 0.001] with an adjusted HR of 2.34 (95%CI 1.33–4.12, p = 0.003).

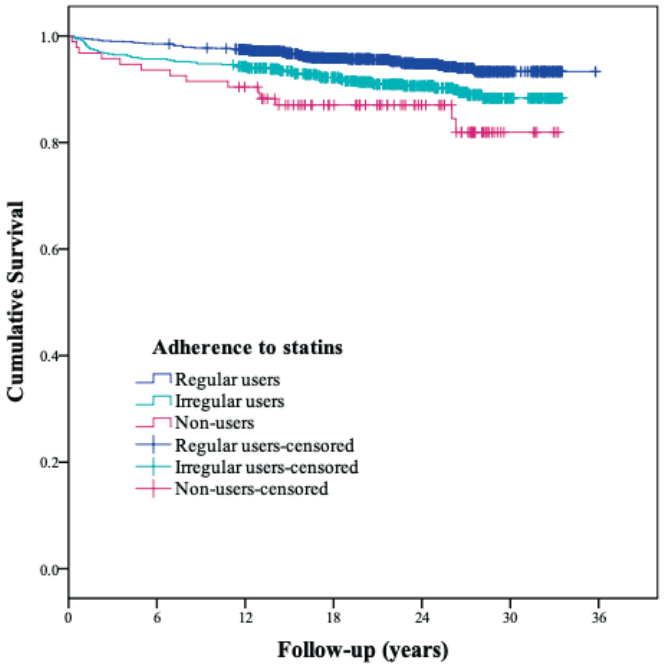

Figure 5 **Univariable Kaplan–Meier proportional propability of survival curves for secondary adherence to statins.** Adapted from Allonen et al. (2012), reprinted with permission from John Wiley & Sons.[361]

In the sensitivity analyses, the effect was otherwise similar, although with a 90-day interval, we observed no significant difference in mortality due to the low number of regular users. Absolute mortality was significantly lower amongst regular users with no intervals greater than 120 (3.7%, $p < 0.001$) and 150 days (3.9%, $p < 0.001$) compared to nonusers (14.9%).

5.3.2 β-BLOCKERS (STUDY III)

We investigated the survival benefit from adherence to each of the secondary prevention medications separately in a univariable Cox proportional hazards models for both primary and secondary outcomes. Table 5 presents the hazard ratios for these analyses. Since clopidogrel is usually prescribed only for the first year following an ACS event, we assessed it as a non-time-dependent variable in survival analyses. In a multivariable confounder-adjusted survival analysis, we found that nonadherence to β-blockers associated with an increased risk of all-cause mortality in terms of overall survival (OS) [HR 1.84 (95% CI 1.51–2.24, $p < 0.001$] and on 1-year landmark survival (1YLS) [HR 1.74 (95% CI 1.41–2.14, $p < 0.001$]. Likewise, the risk of coronary mortality also increased with nonadherence to β-blockers [OS: HR 1.67 (95% CI 1.24–2.26, $p = 0.001$; 1YLS: HR 1.55 (95% CI 1.12–2.14, $p = 0.008$; see Table 7). In a sensitivity analysis, using adherence as a three-category variable ranging from good, intermediate and poor, the stepwise increase in HR for both all-cause and coronary mortalities remained relativley consistent. Yet, in the 1YLS analysis, the impact of intermediate adherence on coronary mortality was barely statistically nonsignificant. Table 6 summarises the results of the sensitivity analyses.

Table 5. ***Univariable analyses for each secondary prevention medication.*** *Abbreviations: 1YLS, one-year landmark survival; CI, confidence interval; OS, overall survival.*

	ALL-CAUSE MORTALITY		CORONARY MORTALITY	
	OS	1YLS	OS	1YLS
β-blockers	**2.99** (95% CI 2.50–3.57)	**2.71** (95% CI 2.25–3.27)	**2.62** (95% CI 2.01–3.42)	**2.23** (95% CI 1.67–2.97)
Statins	**3.49** (95% CI 2.91–4.17)	**3.20** (95% CI 2.64–3.87)	**2.83** (95% CI 2.17–3.68)	**2.34** (95% CI 1.76–3.11)
RAA inhibitors	**4.06** (95% CI 3.31–4.98)	**4.02** (95% CI 3.23–4.99)	**4.11** (95% CI 3.06–5.53)	**4.01** (95% CI 2.92–5.53)
Clopidogrel	**2.09** (95% CI 1.68–2.61)	**1.89** (95% CI 1.49–2.41)	**2.34** (95% CI 1.69–3.25)	**2.04** (95% CI 1.41–2.96)

In addition to mortality, we also assessed the effect of adherence on rehospitalisations for different reasons during the entire follow-up period. In the univariable Cox regressions, nonadherence to β-blockers increased the risk of rehospitalisations for recurrent MI; HR 1.39 (95% CI 1.05–1.82, p = 0.020); for HF; HR 1.61 (95% CI 1.27–2.03), p < 0.001; for CV diagnoses: HR 1.54 (95% CI 1.27–1.88), p < 0.001 and for non-CV diagnoses; HR 1.16 (95% CI 1.02–1.31), p = 0.019. However, in multivariable models, only rehospitalisations for HF and CV diagnoses were associated with nonadherence to β-blockers [HR 1.57 (95% CI 1.23–2.02), p < 0.001 and HR 1.30 (95% CI 1.05–1.62), p = 0.016, respectively]. HRs for recurrent MI and non-CV diagnoses were 1.16 (95% CI 0.86–1.56, p = 0.332) and 1.10 (95% CI 0.96–1.25, p = 0.179), respectively.

Table 6. ***Multivariable sensitivity analyses for nonadherence to β-blockers.***
Hazard ratios with 95% confidence intervals are presented. Adapted from Allonen et al. (2020) reprinted with permission from Taylor & Francis Group.[360]

	ALL-CAUSE MORTALITY		**CORONARY MORTALITY**	
	Overall survival	**1-year landmark**	**Overall survival**	**1-year landmark**
	Sensitivity analysis, graded adherence			
Good	Reference	Reference	Reference	Reference
Intermediate	**1.53** (95% CI 1.17–2.00)	**1.41** (95% CI 1.06–1.89)	**1.60** (95% CI 1.08–2.36)	**1.49** (95% CI 0.97–2.29)
Poor	**2.55** (95% CI 2.03–3.20)	**2.37** (95% CI 1.87–3.02)	**2.30** (95% CI 1.61–3.27)	**2.12** (95% CI 1.45–3.09)
	Sensitivity analysis, 90-day interval			
Nonadherent	**2.40** (95% CI 1.96–2.93)	**2.24** (95% CI 1.81–2.77)	**2.22** (95% CI 1.64–3.00)	**1.98** (95% CI 1.44–2.74)
	Sensitivity analysis, 120-day interval			
Nonadherent	**1.49** (95% CI 1.22–1.82)	**1.40** (95% CI 1.14–1.73)	**1.30** (95% CI 0.96–1.77)	**1.23** (95% CI 0.80–1.57)

Table 7. ***Multivariable predictors, including nonadherence to β-blockers, for all-cause and coronary mortality on both overall survival and one-year landmark survival.*** *Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention. Adapted from Allonen et al. (2020), reprinted with permission from Taylor & Francis Group.*[360]

	ALL-CAUSE MORTALITY				CORONARY MORTALITY			
	Overall survival		One-year landmark survival		Overall survival		One-year landmark survival	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Nonadherent to β-blockers	1.84 (1.51–2.24)	<0.001	1.74 (1.41–2.14)	<0.001	1.67 (1.24–2.26)	0.001	1.55 (1.12–2.14)	0.008
Nonuse of statins	2.14 (1.76–2.60)	<0.001	2.06 (1.68–2.54)	<0.001	1.70 (1.27–2.27)	<0.001	1.55 (1.13–2.12)	0.006
Nonuse of ACEi/ARB	2.06 (1.70–2.51)	<0.001	2.11 (1.71–2.61)	<0.001	2.09 (1.57–2.80)	<0.001	2.08 (1.52–2.85)	<0.001
Heart failure	3.33 (2.76–4.01)	<0.001	3.16 (2.59–3.86)	<0.001	6.21 (4.68–8.24)	<0.001	5.69 (4.18–7.75)	<0.001
Age	1.06 (1.05–1.07)	<0.001	1.06 (1.05–1.07)	<0.001	1.04 (1.03–1.06)	<0.001	1.05 (1.03–1.07)	<0.001
Diabetes	1.53 (1.26–1.86)	<0.001	1.45 (1.18–1.79)	0.001	1.99 (1.51–2.63)	<0.001	1.95 (1.44–2.64)	<0.001
Atrial fibrillation	1.52(1.20–1.91)	<0.001	1.64 (1.28–2.10)	<0.001	1.39 (0.99–1.94)	0.057	1.58 (1.10–2.27)	0.013
Previous MI	1.42 (1.17–1.72)	<0.001	1.40 (1.14–1.72)	0.002	1.59 (1.20–2.10)	0.001	1.69 (1.24–2.28)	0.001
Triple vessel disease	1.19 (0.97–1.44)	0.091	1.19 (0.97–1.47)	0.099	1.26 (0.94–1.68)	0.120	1.21 (0.89–1.66)	0.226
Thrombolysis	0.71 (0.49–1.03)	0.069	0.76 (0.52–1.11)	0.150	0.25 (0.10–0.60)	0.002	0.30 (0.13–0.67)	0.004
Kidney disease	1.76 (1.18–2.61)	0.005	1.92 (1.26–2.93)	0.002	1.19 (0.63–2.27)	0.590	1.27 (0.62–2.60)	0.518
Hypertension	1.31 (1.06–1.60)	0.011	1.35 (1.09–1.69)	0.007	1.34 (0.98–1.84)	0.069	1.34 (0.95–1.89)	0.098
PCI	0.84 (0.69–1.02)	0.078	0.82 (0.67–1.01)	0.063	0.84 (0.63–1.12)	0.243	0.80 (0.59–1.10)	0.165

5.3.3 NSAIDS (STUDY IV)

During follow-up, 48.7% (n = 935) of those patients still living 30 days following CAG suffered the composite endpoint of a recurrent MI or death. Amongst these, 29.7% (n = 570/1919) experienced a recurrent MI as the end event during follow-up, whilst 19.0% (n = 365/1919) of patients died. The mean survival time until the end event was 6.2 years (SD ± 3.2 years). Recurrent MI occurred sooner on average than death [3.1 years (SD ± 2.5 years) and 4.1 years (SD ± 2.8 years), respectively].

We observed no significant difference in the incidence in the composite outcome when we compared current NSAID users to nonusers in absolute figures [53.4% (n = 47) vs. 48.5% (n = 888)] or in a univariable logistic regression [OR 1.22 (95% CI 0.79–1.87), p = 0.369]. In a multivariable adjusted logistic regression, however, current NSAID use associated with a increase in the risk of recurrent MI and death [OR 1.75 (95% CI 1.10–2.78), p = 0.019; Figure 6).

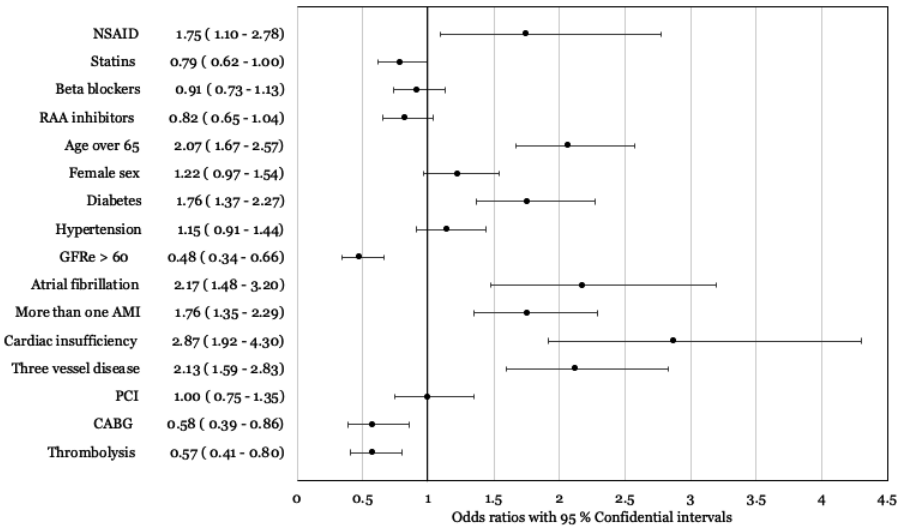

Figure 6 Multivariable predictors of the composite endpoint in a logistic regression model.

In the sensitivity analyses, 71 (3.7%), 124 (6.5%) and 120 (6.3%) patients were defined as current users, using twice the DDD, half the DDD and a days' supply end cut-off of 60 days to categorise groups, respectively. As in the primary analyses, we found no significant impact on survival in univariable analyses with the sensitivity definitions either. However, in multivariable logistic regressions using half the DDD definition and '60- days' definition, NSAID use increased the risk of outcomes [OR 1.53 (95% CI 1.03–2.28), p = 0.036 and

OR 1.62 (95% CI 1.08–2.43), p = 0.019]. OR for twice the DDD definition was 1.60 (95% CI 0.96–2.69, p=0.073).

5.3.4 LOW- AND HIGH-RISK PATIENTS

In studies III and IV, we further analysed the effects of β-blockers and NSAIDs, respectively, amongst subgroups of low- and high-risk patients. In study III amongst high-risk patients, nonadherence to β-blockers associated with an increased risk of both all-cause mortality and coronary mortality in OS and 1YLS. In addition, an increased risk for readmission due to HF although not for other reasons also associated with nonadherence to β-blockers amongst both risk groups [for high-risk patients: HR 1.62 (95% CI 1.06–2.49), p = 0.026; and for low-risk patients: HR 1.60 (95% CI 1.18–2.18), p = 0.003]. Yet, amongst low-risk patients, both OS and 1YLS, only an increased risk of all-cause mortality but not coronary mortality accompanied nonadherence to β-blockers. Table 8 summaries the HRs for nonadherence to β-blockers calculated from the multivariable models within each risk group.

Table 8. ***Nondherence to β-blockers amongst low- and high-risk patients****. Hazard ratios with 95% confidence intervals in multivariable survival analyses for primary and secondary outcomes based on overall survival and one-year landmark survival analyses.*

	ALL-CAUSE MORTALITY		CORONARY MORTALITY	
	Overall survival	**1-year landmark survival**	**Overall survival**	**1-year landmark survival**
High risk	**2.03** (95% CI 1.58–2.61)	**1.92** (95% CI 1.47–2.51)	**1.84** (95% CI 1.29–2.62)	**1.67** (95% CI 1.14–2.45)
Low risk	**1.60** (95% CI 1.16–2.21)	**1.57** (95% CI 1.12–2.20)	**1.37** (95% CI 0.77–2.45)	**1.32** (95% CI 0.71–2.46)

The trends in use of prescribed NSAIDs following ACS in study IV mirrored the main cohort in both risk groups. At least one prescription per year was filled in the first year by 18.4% (n = 207) of low-risk and 16.7% (n = 133) of high-risk patients, by 24.4% (n = 269) and 18.5% (n = 136) in the second year and by 16.7% (n = 163) and 10.0% (n = 50) of low- and high-risk patients, respectively, in the eighth year. In total, 62 (5.5%) patients were defined as current NSAID users within the low-risk group, amongst whom NSAID use was associated with an increased risk for recurrent MI and death in multivariable logistic regression analysis [OR 2.03 (95% CI 1.19–3.48), p =

0.010]. Amongst high-risk patients, current NSAID use (n = 26, 3.3%), however, did not significantly affect survival [OR 1.19 (95% CI 0.50–2.85), p = 0.697].

5.4 RED BLOOD CELL TRANSFUSIONS (STUDY II)

A total of 85 previously transfusion-naïve, non-CABG patients who survived at least 30 days following CAG received at least one RBC transfusion during the index hospitalisation. Overall, they received a median of 8 (IQR 2–9) international units (IU) of packed RBCs cumulatively, the first of which was transfused at a mean of 5.6 (SD ± 6.3) and 4.2 (SD ± 6.2) days following admission and CAG, respectively. Table 9 summaries the primary indications for transfusion. RBC-transfused patients, in general, were older and sicker than those who did not receive any transfusions (n = 1278). They more often presented with hypertension, DM, FA, CKD, a prior cancer, more severe CAD and were more often anaemic females. Other than the Hb values, no significant differences were observed following 1:1 propensity-score matching. The propensity matching achieved both a good statistical discrimination and adequate covariate balance [C-statistic: 0.91, (95%CI 0.88–0.94) and Hosmer–Lemeshow, chi-square 3.64, p = 0.888].

Table 9. ***Primary indications for red blood cell transfusion.*** *Abbreviation: LAD, left-anterior descending coronary artery. Adapted from Allonen et al. (2018) reprinted with permission from Elsevier.*[362]

Primary indications for transfusion	**n**	**%**
Not available	36	42.4 %
Coronary angiography access site (femoral) hemorrhage	26	30.6 %
Gastrointestinal bleeding	7	8.2 %
Perioperative transfusion (related to, i.e., a vascular procedure)	5	5.9 %
Chronic anaemia	4	4.7 %
Retroperitoneal haematoma	2	2.4 %
Haematuria	2	2.4 %
Peritoneal bleeding	1	1.2 %
Cancer related	1	1.2 %
Procedure complication (LAD rupture)	1	1.2 %
Total	**85**	**100** %

5.4.1 THE EFFECT OF RBC TRANSFUSION ON LONG-TERM MORTALITY

Before matching, overall mortality amongst patients treated with RBC transfusion was almost threefold higher compared to nontransfused patients [58.8% (n = 50/85) vs. 20.3% (n = 259/1278), p < 0.001]. The absolute mortality figures after propensity matching remained twice as high amongst RBC- transfused patients [52% (n = 34/65) vs. 34% (n = 22/65), p = 0.034]. The mean survival times before and after matching revealed similar results as well; 5.9 years (95% CI 5.2–6.7) for RBC patients and 8.5 years (95% CI 8.4–8.6, p < 0.001) for nontransfused patients before matching and 6.3 years (95% CI 5.5–7.1) for RBC patients and 7.6 years (95% CI 6.9–8.3, p = 0.035) for nontransfused patients after matching (Figure 7).

In a multivariable Cox proportional hazards model amongst an unmatched cohort, RBC transfusion associated with a twofold higher risk of death [HR 1.91 (95% CI 1.39–2.63), p < 0.001]. This finding persisted in the 1YLS analysis. Furthermore, after matching with the propensity score itself included as a covariate in the model, RBC transfusion remained independently associated with higher mortality in terms of both OS and 1YLS (Table 11). In an IPTW Cox regression model, yet again, we found an almost twofold increase in the risk of death in both OS [weighted n = 2130.6; HR 1.70 (95% CI 1.11–2.59), p = 0.015] and in 1YLS [weighted n = 2012.0; HR 2.07 (95% CI 1.38–3.11), p < 0.001].

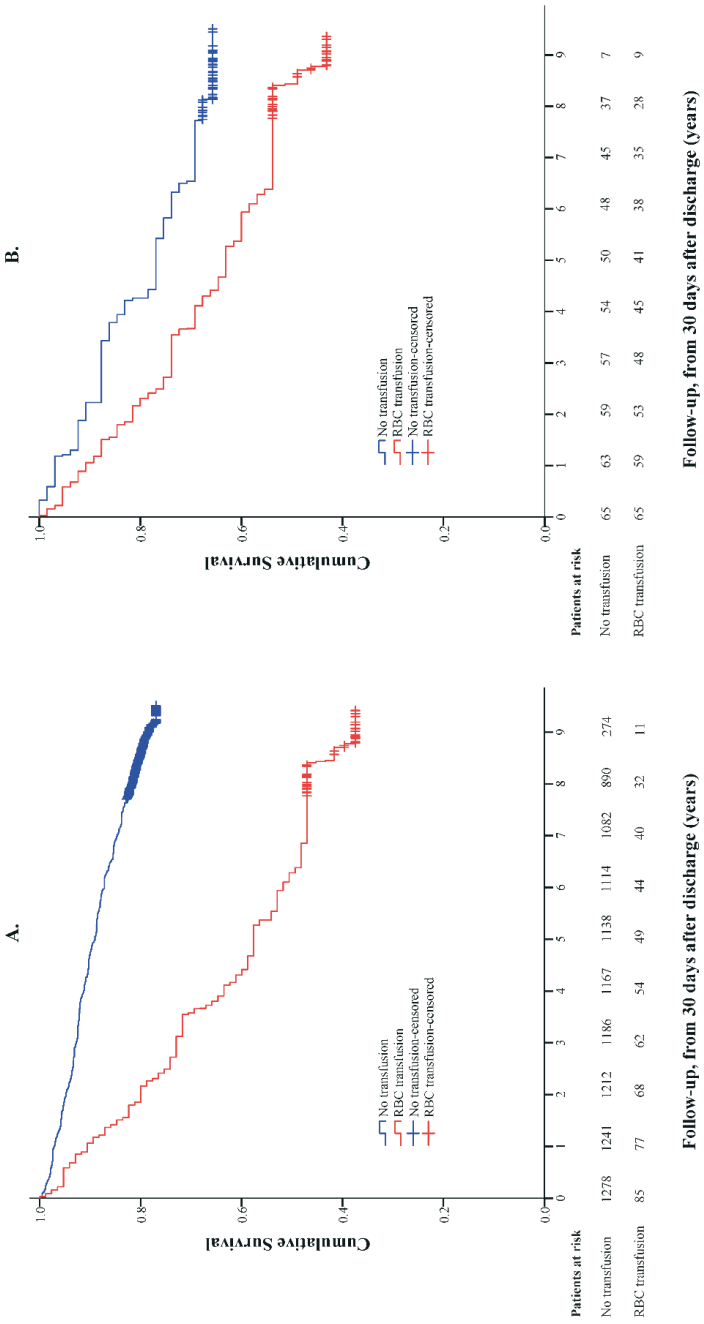

Figure 7 **Kaplan–Meier curves of the estimated mean survival times amongst RBC transfused and nontransfused patients before (A) and after (B) propensity-score matching**. Adapted from Allonen et al. (2018), reprinted with permission from Elsevier.[362]

5.4.2 HAEMOGLOBIN LEVELS AND ANAEMIA

In general, anaemic patients exhibited a greater absolute mortality in the unmatched cohort when compared to their nonanaemic counterparts [45.8% (n = 215/469) vs. 21.4% (n = 239/1116), respectively]. Furthermore, patients with their lowest Hb value during a hospital stay, which fell below 100g/l, increased the risk of mortality compared to those with an Hb level ≥100 g/l [56.1% (n = 97/173) vs. 25.1% (n = 341/1360), p < 0.001, respectively]. The differencies in the Hb levels measured during hospitalisation and later during follow-up between RBC-transfused and nontransfused patients appear in Figure 8.

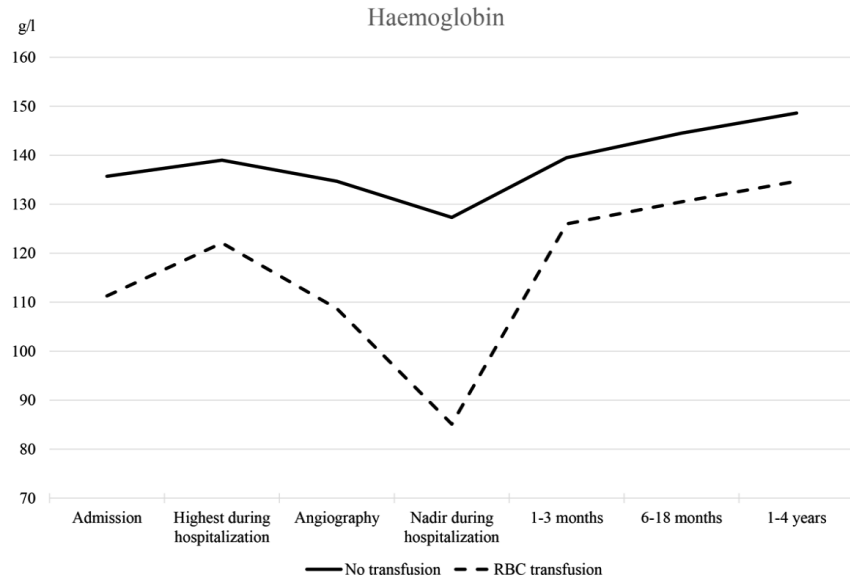

Figure 8 **Mean haemoglobin values amongst both nontransfused and RBC-transfused patients at different timepoints during the course of treatment.** Abbreviations: RBC, red blood cell. Adapted from Allonen et al. (2018), reprinted with permission from Elsevier.[362]

The nadir–Hb in RBC-transfused patients, in turn, fell below 100g/l in 98.8% (n = 84/85) and under 80g/l in 22.4% (n = 19/85) of patients. Amongst RBC-transfused patients, we detected no difference in the mortality figures between patients with nadir–Hb less than or more than 80g/l [57.9% (n = 11/19) vs. 59.1% (n = 39/66), p = 0.926, respectively]. Furthermore, in the multivariable subgroup analyses for both anaemic (n = 344) and nonanaemic (n = 951) patients, RBC transfusion associated with an increased risk of mortality in terms of OS as well as in 1YLS (Table 10).

Table 10. ***The multivariable hazard ratios with 95% confidence intervals on 1-year landmark survival and overall survival for red blood cell transfusion in subgroups of anaemic and nonanaemic patients.*** *Abbreviations: CI, confidence interval.*

	ALL-CAUSE MORTALITY	
	Overall survival	**1-year landmark survival**
Anaemic	**1.55** (95% CI 1.05–2.29)	**1.63** (95% CI 1.07–2.47)
Nonanaemic	**3.57** (95% CI 1.65–7.72)	**3.02** (95% CI 1.22–7.48)

5.4.3 ASSOCIATION WITH CANCER

We further investigated mortality by analysing the causes of death. Cancer (ICD-10: C diagnoses) was surprisingly overrepresented within RBC-transfused patients [15.3% (n = 13/85) vs. 4.1% (n = 52/1278), p < 0.001]. The incidence of new cancer diagnoses amongst transfused patients during follow-up, however, did not differ from that amongst nontransfused patients [19.5% (n = 16/82) vs. 13.1% (n = 165/1262), p = 0.098, respectively]. Yet, RBC transfusion associated with an increased risk of cancer mortality in an age- and smoking-adjusted multivariable Cox regression model [HR 2.89 (95% CI 1.44–5.77), p = 0.003]. For this analysis, we excluded patients diagnosed with cancer prior to the index hospitalisation.

Table 11. ***Multivariable predictors of mortality before and after propensity matching.*** *Abbreviations: CABG, coronary artery bypass grafting; CI, confidence interval; eGFR, estimated glomerular filtration ratio; HR, Hazard ratio. Adapted from Allonen et al. (2018), reprinted with permission from Elsevier.*[362]

	UNMATCHED COHORT				**PROPENSITY SCORE–MATCHED COHORT**			
	Overall survival		**1-year landmark survival**		**Overall survival**		**1-year landmark survival**	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Red blood cell transfusion	1.91 (1.39–2.63)	<0.001	1.90 (1.34–2.69)	<0.001	2.70 (1.48–4.95)	0.001	2.32 (1.20–4.49)	0.013
Atrial fibrillation	1.98 (1.47–2.68)	<0.001	2.06 (1.50–2.85)	0.001	–	–	–	–
Prior myocardial infarction	1.50 (1.16–1.94)	0.002	1.54 (1.17–2.03)	0.002	–	–	–	–
eGFR < 60 (ml/min/1.73 m²)	1.61 (1.24–2.10)	<0.001	1.60 (1.20–2.13)	0.001	–	–	–	–
Diabetes	1.61 (1.25–2.06)	<0.001	1.65 (1.26–2.15)	<0.001	–	–	–	–
Triple vessel disease	1.82 (1.42–2.34)	<0.001	1.73 (1.32–2.26)	<0.001	–	–	–	–
Statins	0.43 (0.28–0.65)	<0.001	0.42 (0.26–0.67)	<0.001	–	–	–	–
Age	1.07 (1.06–1.08)	<0.001	1.08 (1.06–1.09)	<0.001	1.08 (1.04–1.12)	<0.001	1.08 (1.04–1.12)	<0.001
Body mass index	–	–	–	–	1.09 (1.03–1.15)	0.004	1.13 (1.06–1.20)	<0.001
Clopidogrel	–	–	–	–	0.43 (0.23–0.79)	0.006	0.45 (0.23–0.88)	0.020
Prior CABG	–	–	–	–	4.85 (2.30–10.23)	<0.001	4.94 (2.17–11.23)	<0.001
Propensity score	–	–	–	–	2.10 (0.55–7.96)	0.277	1.83 (0.42–8.07)	0.423
Cerebrovascular disease	–	–	–	–	–	–	3.00 (1.28–7.01)	0.012

6 DISCUSSION

In this study of consecutive ACS patients examined using CAG, we defined adherence rates to secondary prevention medications, specifically to statins and β-blockers during an extensive follow-up period. Furthermore, we demonstrated the importance of patients' strict medical behaviour even years after an ACS event enabling a better survival. This study also investigated if ACS patients continue using NSAIDs despite gradually tightened restrictions within guidelines. Additionally, we examined the effect of RBC transfusion on ACS patients' long-term prognosis seeking to understanding the phenomena behind adverse events previously associated with them by examining the incidence of new cancer diagnoses and cancer mortality during follow-up.

6.1 ADHERENCE TO STATINS

All-cause mortality amongst ACS patients was profoundly associated with the level of adherence to statins in study I. The absolute mortality figures for nonadherent patients were threefold higher compared to those amongst regular statin users. These figures are markedly higher than in placebo-controlled trials, although quite consistent with previous observational studies.[151,198,215,363] The increase in the relative risk of death related to the nonuse of statins also remained consistent, although slightly greater compared to studies published both prior to and following our analysis.[17,20,364,365] We observed a stepwise increase in mortality figures associated with the adherence level from regular to intermediate users to nonusers. Moreover, amongst regular statin users, patients with the most regimented refill behaviour exhibited the lowest risk for death. These results reflect both the importance of strictly continuous statin therapy following ACS, as well as the nature of adherence itself. Specifically, the healthy adherer bias possibly affected our results to some extent.

Within our cohort, as many as 95% of discharged patients were prescribed statins. This demonstrates the close compliance with guidelines amongst physicians. In addition to long-term adherence, we assessed primary adherence to statins. Amongst patients with a new statin prescription upon discharge, about 80% filled it within the first week. This agrees with previous studies as well.[17] Interestingly, primary adherence independently associated with both decreased long-term mortality, as well as with increased secondary adherence. Hence, it is of great importance to motivate patients to fill their prescriptions immediately following hospitalization. It seems that if attention is devoted to this moment, patients tend to adhere better to their secondary prevention therapies in long-term as well.[17,214] For instance, nurse-based

reminder calls or appointments could result in greater medical compliance in future.[226,227]

Secondary adherence to statins diminished drastically during follow-up. Whilst about 90% initiated or continued their statin therapy upon discharge, only slightly more than 60% of patients were considered regular statin users throughout a two-year follow-up. These figures are unfortunately quite similar to previous and more recent findings, whereby around 40% to 75% adherence rates emerged at 1- to 2-year landmarks.[16,18,20,179,206,207,366-368] In the last decade, however, it seems that adherence to secondary prevention medications including statins has improved to a small degree.[231,369,370] Still, when compared with the neglible 5-year discontinuation rates of 6% to 19% in landmark secondary prevention trials, these figures appear rather grim.[198,363,371] Furthermore, in study III, which primarily assessed β-blockers, we observed a decrease in yearly adherence rates to statins from nearly 90% during the first year to less than 70% by the eighth year of follow-up amongst surviving patients. Amongst deceased patients, statin adherence decreased even further, from 80% to as low as 43% during the same time frame. Naturally, these figures are not directly comparable to other studies given the varied methods used to estimate adherence rates.

In conclusion, even in Finnish society with a population-wide medical care and reimbursement system, ACS patients' adherence to statins remains unsatisfactory, and nonadherence is associated with a poorer prognosis. Measures should be taken to improve adherence, and attention should specifically focus on the moment of discharge and the first days following discharge to ensure the initiation of life-saving therapies.

6.2 ADHERENCE TO β-BLOCKERS

In our cohort, β-blockers were prescribed to more than 90% of discharged patients. At the time of patient recruitment to this study, the European expert consensus document on β-blockers published in 2004 continued to recommend life-long β-blocker therapy to all AMI patients so long as no contraindications appeared.[232] ESC guidelines for NSTE-ACS published in 2007, however, suggested life-long β-blocker therapy to only ACS patients with decreased LV function, whether symptomatic or not.[372] For patients with preserved LV function, the guidelines did not provide any recommendations, although they stated that long-term β-blocker therapy may lead to a significant reduction in mortality. Moreover, US guidelines from 2004 recommended β-blockers for all STEMI patients excluding low-risk patients (i.e., normal LV function, successful reperfusion and no significant ventricular arrhythmias) for whom prescribing β-blockers was still considered reasonable.[373] Therefore, during recruitment for our study, the recommendations for β-blocker use were already under review. Yet, the rate of β-blocker prescriptions upon discharge

remained quite high in our study. Already in the first year following ACS, we observed a decrease in adherence rates to all secondary prevention medications and the rates continued to plummet until the end of follow-up. These trends mirror previous studies.[15,228,254-256]

In addition, poor adherence to β-blockers asssociated with an increased risk for both all-cause and coronary mortality across the entire ACS cohort. Although we observed a more prominent effect on better survival amongst high-risk patients, good adherence to β-blocker therapy appears beneficial to low-risk ACS patients as well. Although the effect on coronary mortality was not statistically significant, a decreased risk for both all-cause mortality and rehospitalisations due to HF associated with good adherence to β-blockers amongst low-risk patients. Previous studies were more in line with our findings for high-risk patients, although a few recent studies support the finding that low-risk patients irrespective of preseved LVEF also benefit from the continous use of β-blockers.[25,28,29,252,374]

The follow-up period in our study represents one of the lengthiest published to date in the adherence-mortality field, specifically regarding prospective studies. During follow-up, we observed a clear association between nonadherence to β-blockers and an increased risk of negative outcomes even one year following the ACS event in our landmark survival analyses. Prior studies, however, suggest that the prognosis especially amongst low-risk patients, although even amongst ACS patients in general, did not improve with β-blocker therapy one year after an MI. For instance, in a multicentre study by Puymirat el al., the discontinuation of β-blockers after the first year did not increase long-term mortality amongst non-HF ACS patients.[30] Furthermore, Dondo et al. concluded that the mortality of non-HF MI patients does not decrease with β-blocker therapy even during the first year following an MI.[26] Two recent Korean observational studies published in 2020 reported contradictory conclusions from each other. Specifically, one proposed that only patients with lowered LVEF benefit from β-blockers, whilst the other found that β-blocker therapy benefits all ACS patients in a follow-up of at least up two years.[375,376] Obviously, unwavering consensus remains beyond reach. However, our results indicate that continous β-blocker therapy benefits all post-ACS patients, not only during the first year. Some recent observational studies, on the other hand, also support this.[31,32,253]

After adjusting for multiple confounders, including the most prominent indicator of a risk profile, HF, examined as time-dependent variables and with accurate causes of death distinguishing all-cause and coronary mortalities separately, our study using an extensive follow-up carries multiple strengths supporting the results. Moreover, the utilisation of medications and adherence to β-blockers, contrary to most studies, were analysed in a dynamic time-dependent manner, allowing us to better mimic real-life situations.[24] Both of our sensitivity analyses also indicated that even stricter adherence to β-blockers seems beneficial.

As described below, however, our study also carries several limitations. For instance, from this observational study we can only find associations between variables, not establish causal relationships between them. Considering the low-risk patient subgroup, the healthy adherer phenomenon may explain why no effect on coronary mortality contrary to all-cause mortality was observed with β-blocker therapy. For instance, amongst nonadherent low-risk patients, other CV or lifestyle-dependent causes of death might be overexpressed. However, we did not examine this, and it, thus, remains mere speculation. Moreover, the worse prognosis amongst nonadherent ACS patients could, theoretically, be partly explained by β-blocker withdrawal syndrome as opposed to merely the beneficial effects of β-blocker use *per se*. It is more likely that patients discontinuing their β-blocker therapy did so suddenly rather than through a stepwise decrease in their daily dosage. Therefore, it is possible that a nonadherent patient suffered from withdrawal symptoms and succumbed to a recurrent ACS, a ventricular arrhythmia or even an SCD due to the abrupt discontinuation of a β-blocker. Yet, again, this remains unclear and is entirely speculative. Despite much study, particularly prior to the reperfusion era, the position and role of long-term β-blocker therapy following ACS remains inconclusive. Further studies are needed to confirm which ACS patients benefit from continuous long-term β-blocker therapy and which do not.

6.3 RBC TRANSFUSION

Previous studies associated RBC transfusion with an increased mortality up to one year following an ACS event.[334,377,378] Prior to our study, however, results from lengthier follow-up periods remained scarce.[379] In our study, the need for RBC transfusion strongly associated with an increased mortality through the longest follow-up reported, even beyond the first year following discharge. Previous research established that patients treated with RBC transfusion are on average sicker, older and more fragile than patients not needing a transfusion. Our study mirrored those results. As in previous studies, RBC-transfused patients were more often anaemic already at baseline, had more comorbidities such as diabetes and hypertension, experienced more severe CAD and presented with a weaker renal function than nontransfused patients.[335,341,380] However, a recent meta-analysis of STEMI patients indicated that the association with increased mortality could not only be explained by transfused patients' comorbidities.[344] Although no direct causal relationship between RBC transfusion and mortality can be established from our observational study, in order to thoroughly adjust for these confounders and more firmly explain our results, we matched RBC- transfused to nontransfused patients using a propensity score. Ultimately, using the IPTW Cox regression model, we verified the strength of our results.

Yet, the bias from any unmeasured confounding can affect these findings. Furthermore, the main issue in studying the impact of RBC transfusion on prognosis remains whether the cause for any adverse effects is indeed the RBC transfusion itself or the indication for its necessity—that is, the anaemia or bleeding. In our study, we attempted to address this issue in two separate subanalyses. First, we assessed the effect of an RBC transfusion effect on survival in both anaemic and nonanaemic patients, finding that transfusion associated with an increased risk of mortality in both of groups. Second, amongst RBC-transfused patients, we detected no difference in mortality rates when patients with nadir–Hb >80 g/l were compared to those <80 g/l. These results suggest that RBC transfusion would independently affect survival irrespective of either anaemia or nadir–Hb. Previous studies were unable to conclude whether to employ a liberal or restrictive transfusion strategy on ACS patients, although suggestions for more beneficial outcomes relying on a restrictive strategy have been reported.[303,332-336,345] Furthermore, a recent meta-analyses of critically ill ICU patients associated a restrictive strategy (transfusion threshold of Hb <70 g/l) with a diminished risk of MI.[381] Our results lean towards the use of a restrictive strategy, although our findings provide no definitive conclusions.

The underlying mechanisms for the possible causality of RBC transfusion and increased mortality remain unclear, although we may speculate. For instance, storage and packing markedly influence the physical and functional capabilities of RBCs, which may have a detrimental impact on their ability to produce the desired effect of increasing oxygenation.[382] It seems that stored RBCs may also attenuate the effect of nitric oxide produced by the vascular endothelium. This reportedly results in a diminished ability to regulate regional blood flow in zones of ischemia and hypoxia, which naturally plays a crucial role in ACS patients.[383] However, a recent Cochrane review of RCTs concluded that the length of time RBCs are stored does not impact mortality.[384] RBC transfusions may also produce prothrombotic, proinflammatory and immunosuppressive effects. For instance, cytokines such as interleukin (IL)-1, IL-8 and tumour necrosis factor reportedly increase following the transfusion of stored RBCs.[385,386] These can cause several immunomodulatory effects possibly inducing inflammation in coronary plaques and, thus, worsening coronary disease outcomes. Another previously quite scantily investigated explanation of the association between mortality and transfusion may lie in malignant disease.[387,388] Thus, as a secondary analysis, we identified an association in the increased risk of cancer mortality in patients treated with RBC transfusion in our cohort. However, we found no effect on new cancer incidence. Perhaps, RBC transfusion-induced immunomodulatory effects, better known as transfusion-related immune modulation (TRIM), cause a latent or undiagnosed malignancy to progress, as suggested by some studies on cancer surgery.[389] However, a more plausible explanation for this association suggest that, when treated with potent antithrombotic and anticoagulant agents, a patient with a previously

unmanifested tumour such as in the gastrointestinal tract begins to bleed, leading to RBC transfusion and ultimately to a cancer diagnosis. In general, however, we feel that this association should be further examined.

Based on both our own and others' studies, we cannot yet conclude that RBC transfusion causes a poorer prognosis. Yet, whilst evidence mounts, we feel that every possible action should be taken to minimise the need for an RBC transfusion. This could be achieved, for instance, by assessing patient's bleeding risk followed by reducing the dosage of antithrombotic drugs, as well as by favouring radial instead of femoral access in CAG.[298,349-351,390] However, further randomised trials to both clarify the relationship as well as to identify the safest strategies to treat bleeding and anaemic ACS patients with RBC transfusions are warranted.[342]

6.4 NSAIDS

Almost 50% of ACS patients in our cohort filled at least one prescprition for NSAIDs during the follow-up period. Considering that most NSAIDs for short-term use are purchased over-the-counter (OTC) in addition to these filled prescriptions, we believe this figure is alarmingly high amongst coronary patients, although in agreement with previous studies.[45,46,48,391,392] Whilst we observed a slight declining trend during follow-up, the proportion of patients filling at least one NSAID prescription each year remained quite steady at around 15% to 20%. Furthermore, the rate of patients filling three or more prescriptions annually did not significantly decrease with time. As previously stated, studies conducted upon the emergence of coxibs raised a concern regarding the unwanted cardiac effects related to the use of COX-2 inhibitors and subsequently to all NSAIDs. This led to withdrawing rofecoxib from the market in 2004 in the USA and, further, in 2007 to contraindications for all NSAIDs to patients with ischemic heart disease.[42,43] The selection of our cohort between 2006 and 2008 coincided with these events. The somewhat downward trend in NSAID consumption observed in our cohort might reflect the emergence of evidence against their use. Yet, measured as DDDs/1000 inhabitants/day, the OTC utilisation of the most-used NSAID—ibuprofen—in Finland was 23.37 in 2008, based on Finnish medicine statistics.[393] Accordingly, in 2018, that figure was 22.42, reflecting only a miniscule decline, at least at the population level.[394] Moreover, the overall sales figures for ibuprofen to hospitals and pharmacies was 47.46 DDDs/1000 inhabitants/day in 2008, increasing to 49.73 in 2018. In contrast to OTC use, an increase in the trend for overall utilisation of ibuprofen occurred in the last decade. However, whilst rather conclusive evidence has increasingly mounted since then, such that guidelines already recommend avoiding all NSAIDs, we feel that the simultaneous decrease in utilisation rates of NSAIDs in our ACS cohort is insufficient.[117]

As anticipated from previous findings, we observed an increased risk for a composite endpoint of recurrent MI or death amongst current NSAID users in our multivariable analyses.[36,265,266,285,286,395-397] However, we did not observe this effect in the absolute figures nor in our univariable analyses. Results from sensitivity analyses were similar. In our multivariable models, we adjusted for multiple confounding factors, including concurrent secondary prevention medications. Our study also benefited from the inclusion of only ACS patients diagnosed with CAG during an exceptionally lengthy follow-up period. However, our findings on the effect of current NSAID use on the composite outcome remains rather inconclusive given the discrepancy between our results from univariable and multivariable analyses. This is further addressed in the limitations section.

That said, we further analysed the effect of NSAID use on the composite outcome in subgroups, finding a similar association between current NSAID use with a poorer outcome only amongst low-risk patients and in the multivariable analysis. The number of patients in the high-risk subgroup remained quite low, possibly partially explaining the nonsignificant result, although this finding might reflect nonadherence to guidelines amongst physicians. For instance, if a patient presents as otherwise healthy without major risk factors and suffered only one minor MI, NSAIDs might be misconsidered as a safe pain medication for them.[44] In our cohort, we measured NSAID use as filled prescriptions, which was apparently more common amongst low-risk patients. Naturally, this is merely speculation and does not respresent a definitive conclusion to our study. However, to narrow the gap between evidence and practice, we feel that ACS patients should be reminded both during and after hospitalisation, if possible, to steer clear of NSAID use regardless of duration, the agent intended for use, dosage or the patient's own residual risk.[46,267,283,398,399]

6.5 LIMITATIONS OF THE STUDY

Despite the many strengths of this study, including the extensive follow-up time amongst unselected, consecutive and angiographed ACS patients, this type of observational study carries specific limitations as well. Our cohort was collected from a university teaching hospital and consists of only Caucasian patients. This limits the generalisability of our findings. Yet, our cohort benefits from being prospectively gathered and unselected, with an exceptionally wide age range. In an observational study, one of the primary limitations stands as the bias in unmeasured confounders. Therefore, we can not establish causal relationships based on this type of study. However, trends and associations between interventions and outcomes after adjusting for multiple crucial variables were observed. In addition to these general limitations, in study II, one definite drawback consists of the lack of definitive

data on bleeding events and indications for RBC transfusion. In addition, we failed to incorporate data on laboratory samples regarding patients' iron status, for example, ferritin and transferrin. Therefore, we were unable to investigate the effect of iron deficiency or the role of iron replenishment following RBC transfusion on transfused patients' survival.

Specific limitations also emerge when assessing the utilisation of and adherence to medications. First, data on medication usage are based on prescriptions filled and the time intervals between them, solely used as a logical proxy indicator of continuous medication use and not guaranteeing the actual consumption of a drug. The latest methods used in adherence studies, namely, 'proportions of days covered' or 'medication possession ratio' could not be employed due to the absence of information in SII's Finnish Prescription Register on prescribed dosages. Second, in both studies I and III, the interval allowed between prescription refills was based on the assumption that a patient fills the prescription for the maximum reimbursement time they are entitled to, which stands at three months in Finland. In study I, the interval allowed was 180 days in the primary analyses, a quite loose definition for good adherence. In study III, adherence was measured differently, although an interval of 100 days was allowed in the case of a death. This measure should be more accurate if based on reimbursement time. However, in both cases due to definitions, a patient may have been falsely categorised as adherent whilst truly being nonadherent because of a possibly smaller supply of the refill. Yet, this should dilute rather than accentuate the positive effect of the adherence observed in our outcomes. This was also addressed in the sensitivity analyses. Third, we were unable to identify patients discontinuing medication based on a considered decision by a physician due to adverse or other effects in either of the adherence studies (studies I and III). Instead, these patients were categorised as either irregular users in study I or nonadherent patients in study III. Moreover, we were unable to further investigate the reasons for discontinuing statins or β-blockers. Furthermore, in study III, we did not examine patients who were prescribed β-blocker therapy later during follow-up (that is, no prescription upon discharge). In study I, on the other hand, we were unable to assess the impact of statin use on cholesterol levels, namely, LDL-C during follow-up. Statins in study I, all secondary prevention medications in studies III and IV and NSAIDs in study IV were assessed as pooled pharmacological groups based on ATC codes rather than as individual medical agents, resulting in certain limitations to the interpretation of our findings. This specifically applies to COX-1 and COX-2 inhibitors in study IV. In studies I and III, given that we assessed medications as pooled pharmacological groups, we did not identify patients who switched from one specific medical agent to another within the same medical group. Finally, as previously described, the healthy adherer bias always persists in adherence studies. In other words, patients who adhere to a certain medical therapy also lead to an otherwise healthier life, using other drugs more responsibly and generally taking better care of their well-being.

Additionally, we were unable to examine the OTC purchase of aspirin in study III and NSAIDs in study IV. Nonetheless, we argue that by assessing NSAID use with information on filled prescriptions rather than OTC purchases (which is not possible through Finnish registries) we could more accurately depict the continuous use of these drugs and determine the user status immediately prior to the outcome event. However, given the lack of information on the prescribed dosage, we estimated the days' supply using the DDD values, which in turn created some uncertainties in our definition of a current NSAID user. Moreover, we did not know for which ailment patients used NSAIDs. Furthermore, we assessed the concomitant use of secondary prevention medications only based on the last refill using a similar DDD manner. This represents a suboptimal method, although it is better than nothing when attempting to adjust for any confounding factors. As stated previously, the discrepancy in the results from study IV in the univariable and multivariable analyses limits our certainty related to the findings on the effect of current NSAID use on recurrent MI or death. This discrepancy may be explained by a bias from unmeasured confounders, possibly causing a hidden multicollinearity in the regression analysis. However, we detected no multicollinearity between the variables included in our final models using the VIF values. In any case, our primary goal in study IV was to investigate the behaviour of NSAID utilisation in the years following an ACS event, which we achieved.

In study III we were unable to investigate the effect of β-blocker withdrawal syndrome on nonadherent patient survival. Moreover, we could not identify the proportion of SCD in the long-term mortality of ACS patients. Although we assessed HF as a time-dependent variable in study III, we could not adjust for the LVEF values in the multivariable analyses in any of the studies, since so many patients had missing values given that echocardiography was not routinely performed on every patient.

Our subgroup results in studies III and IV are limited only to the subsets of patients with the conditions included in the risk profile definition. High-risk patients were defined as having one or more of the following: heart failure at baseline, triple vessel disease in CAG or a previous MI. Patients without any of these were definied as low risk.

6.6 FUTURE PERSPECTIVES

To summarise, our results indicate that ACS patients benefit from long-term statin and β-blocker therapy, provided that they adhere to their continuous use without gaps in refilling prescriptions. It seems that years after an MI, patients should continue to avoid even short-term NSAID use. Our results also suggest that physicians should attempt to treat such patients using RBC transfusion only if necessary, to further improve the long-term prognosis of ACS patients. Given the nature of our observational study, however, these

trends and associations do not lead to definitive conclusions from this study. However, these findings provide a solid foundation for future studies.

For all other subgroup of patients beyond ACS patients, guidelines for the safe use of RBC transfusions have been defined, and primarily indicate a restrictive transfusion strategy. Strong evidence supports RBC transfusion for ACS patients with Hb <80 g/l, whilst this is not indicated for patients with Hb >100 g/l.[342,343] However, that inconclusive area causes confusion amongst physicians. Therefore, to clarify this issue, we argue that ACS patients with Hb between 80 g/l and 100 g/l should be randomised to either receive RBC transfusion or not. This could minimise the bias in the treatment indications, including for anaemia or bleeding. Furthermore, both guidelines and physicians have traditionally quite generally used an Hb-level cut-off as the indication for an RBC transfusion. However, most probably patient- specific individual characteristics such as age, comorbidities, sex, baseline Hb levels and chronic anaemia amongst others impact patients' tolerance to a decline in Hb levels. Therefore, question is, whether we should measure instead the delta for the decline in Hb from baseline to nadir and make individual decisions to transfuse based on, for example, a validated risk score or is it safer to use familiar Hb trigger levels for all patients.[400] Additionally, the association between RBC transfusion and cancer mortality should be further investigated. Furthermore, the effect of iron deficiency on prognosis amongst patients needing an RBC transfusion as well as the role of iron replenishment following a transfusion should be addresed in more depth in future.

When it comes to adherence to secondary prevention medications, further knowledge on the multifactorial phenomena behind nonadherence should be examined. More individually targeted interventions should be investigated, preferably through RCTs, to improve adherence. Considering long-term β-blocker therapy in ACS patients' secondary prevention an RCT amongst prespecified low-risk patients with preserved LV function should be conducted along with the utilisation of medications further adjusted with as precise of an adherence measure as possible. The β-blocker withdrawal syndrome should also be taken into consideration as a possible phenomenon explaining the poorer prognosis of nonpersistent patients. Interestingly, the BETAMI trial has already begun recruiting patients and the trial protocol appears quite promising.[401] This randomised multicentre study amongst 10 000 MI patients treated with PCI or thrombolysis with LVEF ≥40% or no clinical signs of heart failure should examine the superiority of β-blocker therapy compared with no β-blocker therapy in relation to all-cause mortality or recurrent MI over a mean follow-up of 3 years. Hopefully, this long-standing mystery will finally be unraveled.

7 CONCLUSIONS

We can draw the following conclusions based on these studies:

1) The adherence rate to statins following ACS remains insufficient. In addition, a stepwise decrease in adherence to statins correlates with a corresponding increase in mortality. Patients initiating statin therapy soon after discharge appear to have better odds of remaining regular users and achieving a better prognosis as well.

2) The association between increased long-term mortality and the need for RBC transfusion during acute treatment for an ACS event amongst non-CABG patients is evident. This association remains strong even after the first year of follow-up.

3) The adherence rate to secondary preventive medications decreases drastically every year following an ACS event. Poor adherence to β-blockers amongst ACS patients associates with an increased risk of long-term mortality long after the event, even beyond the first year. The prognostic effect is more evident amongst high-risk patients, although continous β-blocker therapy appears to decrease the risk of both all-cause mortality and rehospitalisations for HF amongst low-risk ACS patients as well.

4) Despite wide evidence on the risks to cardiac patients, NSAIDs are still prescribed to and used by an alarmingly high number of patients following an ACS event. The utilisation rate does not significantly decrease even several years after an ACS. The use of NSAIDs seems to associate with an increased risk of recurrent myocardial infarction and death after an ACS event in multivariable analyses.

8 ACKNOWLEDGEMENTS

This thesis was carried out at the Heart and Lung Centre at Helsinki University Central Hospital (HUCH). I extend my thanks to all who made this work possible during the last decade. This project was financially supported by the Aarno Koskelo Foundation, the Finnish Foundation for Cardiovascular Research, the Finnish Cardiac Society, the Finnish Society of Angiology, the University of Helsinki and the Hospital District of Helsinki and Uusimaa.

First and foremost, I extend my deepest gratitude to my supervisor, Professor Juha Sinisalo, for his tenacious and supportive guidance throughout this project. Juha has always had faith in me, even during times when I struggled with this work. Juha's inspirational way of thinking forward and his positive attitude combined with constructive and continually praising feedback sustained me. Moreover, Juha's expertise in both clinical practice and scientific work has helped me navigate multiple obstacles as I finalised this thesis. As the project comes to an end after more than a decade of collaboration, I am humbled by this experience and opportunity. I also extend my sincere appreciation to my second supervisor, Professor Markku Nieminen. Markku motivated and supported me throughout the years by sharing his execptional experience and expertise in the fields of cardiology and research.

I also wish to thank the reviewers of this thesis, Docent Riikka Lautamäki and Associate Professor Juha Perkiömäki, for their valuable comments and demands to continually improve this thesis. I also wish to thank Vanessa Fuller for editing the language of this thesis. My warm thanks also go to the patients who volunteered to particiatipate in this study, thereby enabling this research.

I also extend my sincerest gratitude to my collaborators Markus Perola, Timo Strandberg, Maisa Lokki, Tero Hiekkalinna, Olavi Parkkonen, Satu Vaara, Seppo Hiippala and Jari Haukka. Without their knowledge, expertise and consultations, this work would have been nearly impossible.

I am grateful to my surgery colleagues in the Gastrointestinal Surgery Department of Jorvi Hospital (HCUH). In particular, I thank both Mervi Javanainen and Hanna Lampela for encouraging me to push forward and finalise this thesis in the middle of challenging times at work. I also owe enormous gratitude to my superior, Leena Halme, for allowing me to straddle between scientific and clinical work throughout this project. I would not have completed this thesis without that flexibility.

My friends deserve special thanks for being in my life and offering a joyful counterbalance to my scientific and clinical work. My closest research colleagues during time, Olavi and Patrick, whose exemplary work motivated me to finally complete my thesis as well, and I thank them both. In particular, I want to thank my brother-from-another-mother, Aleksi, for his life-long

friendship, brotherly competition and endless conversations about science, as well as everything else.

My parents, Matti and Hannele, I thank for everything. They have always supported me in every possible way, through every turn in my life—I cannot emphasise just how important that has been to me. Thank you to my loving and supporting siblings, Mikko and Laura—our exceptional sibling bonds are priceless to me.

Finally, to my dear Roosa, the love of my life, I wish to express my utmost and deepest thanks for her loving support and endless positive encouragement and belief propelling me towards completion of this work. She has always had the strength to listen to my problems, ease the agony and find light at the end of the darkest tunnel through her positive attitude. All of this has truly made this work possible. And, to our wonderful daughter, Enna, whose emergence into this world was the final driving force pushing me to see this thesis to its completion. They both remind me to focus on the essentials in life and to keep my feet firmly planted on the ground. They are my love, my everything.

Espoo, September 2020

Jaakko Allonen

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